

Aus dem Institut für Tierzucht und Tierhaltung
der Agrar- und Ernährungswissenschaftlichen Fakultät
der Christian-Albrechts-Universität zu Kiel

**MODELLING THE EPIDEMIOLOGY AND
CONTROL OF FOOT AND MOUTH DISEASE
WITH SPECIAL EMPHASIS ON
AIRBORNE SPREAD**

Dissertation
zur Erlangung des Doktorgrades
der Agrar- und Ernährungswissenschaftlichen Fakultät
der Christian-Albrechts-Universität zu Kiel

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Tag der mündlichen Prüfung: 8. Mai 2008

Die Dissertation wurde mit dankenswerter finanzieller Unterstützung der Uelzener Allgemeinen Versicherungsgesellschaft a.G., VGH Versicherungen, Westfälische Provinzial Versicherung, Bayerischer Versicherungsverband und der Landwirtschaftlichen Rentenbank angefertigt.

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General Introduction

Foot and mouth disease (FMD) is a highly contagious animal disease and can infect all cloven-hoofed animals, such as cattle, pigs and sheep (Donaldson et al., 2001). The foot and mouth disease virus (FMDV) has the ability to infect in small doses, a rapid rate of replication, and a high level of viral excretion (Alexandersen et al., 2003). As FMDV spreads rapidly and widely, it is classified as an *OIE list A* disease. FMDV belongs to the *Aphthovirus* genus as a member of the *Picornaviridae* family (Alexandersen et al., 2003). Seven distinct serotypes (A, O, C, Asia 1, and SAT (South African Territories) 1, 2, 3) have been identified, and multiple subtypes occur within each serotype (Bachrach, 1968). Outbreaks of FMDV have resulted in severe economic losses in recent years. During the 2001 epidemic in the UK more than 2,000 farms with approximately ten million animals were culled (Kitching et al., 2006). The total losses from agriculture and in the food chain as well as compensation for slaughtered animals and clean-up costs added up to £5.6 billion (Gloster et al., 2003).

Since 1992 regular vaccination against FMD is prohibited in the EU (Anonymous, 2003). Consequently, the animal populations are 100 % susceptible and in case of a virus introduction a rapid and wide spread can be expected. In most regions of the world international trade of live animals (livestock, exotic pets, zoo animals) and of animal products is increasing. This remains the primary risk for the spread of FMD and no country is safe from the introduction or re-introduction of the disease.

After FMDV introduction into a country, effective control strategies for a rapid eradication are necessary. Current legislation in the EU, laid down in the EU Directive 2003/85/EG (Anonymous, 2003), recommends the establishment of movement restrictions in designated areas (protection and surveillance zone), as well as contact tracing and culling of dangerous contact herds. In recent epidemics in Italy (1993), Greece (1994, 1996, 2000), the UK, Ireland, France and the Netherlands (2001) additionally preventive culling was used to eradicate the FMD epidemics. In the Netherlands 2001, soon after the first

outbreak, the culling and destruction capacity was insufficient to depopulate all farms (Barnett et al., 2002; Pluimers et al., 2002; Grubman, 2005). Additionally, an emergency vaccination was established to overcome the shortfall in the destruction capacity. Emergency vaccination was suggested as an alternative to preventive culling not only to avoid limited destruction capacities. It is also favourable from an ethical point of view. The majority of the preventively culled animals in the Netherlands was not infected with FMDV. Moreover, culling for welfare purposes such as overcrowding and compromised nutrition can be ceased (Kitching et al., 2006). In general, legislation provides the control measure emergency vaccination to eradicate FMD epidemics, but demands the approbation of an emergency vaccination plan before the vaccination campaign starts (Anonymous, 2003). Nevertheless, previous FMD outbreaks have shown, that preventive culling is an effective strategy to keep the virus spread under control. As described, the combination of preventive culling and emergency vaccination succeeded in eradicating the FMD outbreak in the Netherlands 2001. Up to now emergency vaccination has never been applied as a single control strategy. Real experiments to compare these control strategies are not feasible. They would last for months or even years and may even be too risky.

Simulation models offer the opportunity to evaluate different control strategies in an acceptable time period and without any risk. Models have been developed to describe the epidemiology and control of FMD. Mostly state-transition and Monte-Carlo simulation models have been applied. Heterogeneity and contact structures are incorporated into Monte-Carlo simulation models and compared to state-transition models allow a more realistic description of the epidemiology of an animal disease. Spatial and temporal elements can be included and farms can be differentiated according to their livestock, animal numbers, and geographical co-ordinates. Consequently, virus spread on a daily basis and distance-dependent virus spread via different transmission modes can be modelled separately.

The most common transmission mode is the introduction of an infected animal into a population of susceptible animals. The virus can be transmitted directly from one animal to another. Indirect virus spread via infected meat or milk as well as mechanical transmission by vehicles and people is also likely. Moreover, FMDV can be transmitted by wind (Donaldson et al., 2001; Alexandersen et al., 2003).

The airborne spread of FMDV has been modelled in special models, such as the Gaussian Dispersion model or the Lagrangian Particle model (Gloster et al., 2003; Sørensen et al.,

2000; Mayer et al., 2007). Only Harvey et al. (2007) incorporated airborne spread into their animal disease spread model. They modelled airborne spread up to 1 km, although it was likely up to 10 km.

Furthermore, existing epidemiological models for FMD represent outbreaks in certain countries or regions (Ferguson et al., 2001a,b; Bates et al., 2003; Kobayashi et al., 2007; Harvey et al., 2007). It is difficult to extrapolate experience of one country to another (Schoenbaum and Disney, 2003). Farm densities, farm sizes, and contact structures are different. Consequently, not only the output but also the simulation models themselves are rarely transferable without any loss of accuracy.

The aim of the present study was to model the epidemiology and control of FMDV in selected regions in Germany. Simultaneous estimation of airborne spread were to be incorporated into the model. By means of the simulation model actual control strategies were to be evaluated. Focus was put upon preventive culling and emergency vaccination strategies with special regard to selective risk factors influencing the effectivity of the control strategies

Chapter One describes the developed spatial and temporal Monte-Carlo simulation model. The virus spread between farms was simulated on a daily basis. Virus transmission was categorised as direct animal transport, indirect contacts with the veterinarian, animal feed vehicle and bulk milk tanker as well as airborne spread. Different control strategies according to the EU Directive 2003/85/EG (Anonymous, 2003) were implemented. In addition to existing models (Bates et al., 2003; Kobayashi et al., 2007), the airborne spread of the virus was estimated simultaneously with a Gaussian Dispersion model. Moreover, contacts between farms were modelled as a routing problem, solved with a Nearest-Neighbour Algorithm.

The validation of the simulation model is the topic of Chapter Two. A sensitivity analysis with a fractional factorial design was performed to evaluate the robustness of the model. Individual risk factors and the corresponding two-factor interactions were estimated. As response variables the epidemic duration as well as the number of infected and culled farms were chosen.

In Chapter Three the simulation model is used to compare the control strategies preventive culling and emergency vaccination. To determine optimal sizes for the eradication strategies, both were established in circles of different size around diagnosed farms. Additionally, the influence of the presence of airborne spread, the farm density, the type of

the index case and the delay of the establishment of the control strategies were taken into account. Interactions between the control strategy and these additional factors were estimated, as recent studies (Morris et al., 2001; Rivas et al., 2003) and the results of Chapter Two suggested. Farm data used in the present study represented a region in Northern Germany.

Finally, in Chapter Four, a Fuzzy-Logic inference system to estimate the spread of FMDV is presented. The Gaussian Dispersion model provides a good approximation for airborne virus spread but does not take topography, changing wind direction and relative humidity into account. Lagrangian Particle models incorporate topography and time-variant meteorological conditions and provide a better estimation of the airborne spread of FMDV (Mayer et al., 2007). Unfortunately, the Lagrangian Particle model needs a variety of weather input parameters, which are hard to measure and estimate, respectively. The aim of the fourth chapter was to create a simple Fuzzy-Logic model based on datasets of weather parameters that could be collected as easily as possible in order to estimate FMDV transmission.

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Chapter 1:

A spatial and temporal Monte-Carlo simulation model of foot and mouth disease epidemics: I. Description of the model

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Abstract

A spatial and temporal Monte-Carlo simulation model was developed to analyse the epidemiology and control of foot and mouth disease. The foot and mouth disease virus could be transmitted by direct animal-to-animal contact, indirect contacts with the bulk milk tanker, veterinarian and animal feed vehicles, via the air and locally. The transport of animals was modelled by contract selling or random distribution via trade. Indirect contacts were described as a routing problem solved with the Nearest-Neighbour Algorithm. Airborne transmission was estimated with a Gaussian Dispersion model. Control measures according to the EU Directive (2003/85/EG) were incorporated and could be combined arbitrarily. The model allowed the determination of risk factors and optimal control measures depending on different contact structures, farm densities and index case types. An example for a region in Northern Germany with 729 farms and a farm density of $1.05 \text{ farms}/\text{km}^2$ was presented. The response variables mean epidemic duration in days, mean number of infected and culled farms were not normally distributed but two peaked, left or right skewed. Analysis of the response variables to evaluate control options had to take the different distributions into account.

Keywords: Foot and mouth disease, Simulation model, Airborne spread, Contact structure

1 Introduction

Foot and mouth disease (FMD) is a highly contagious *OIE list A* disease that can spread rapidly and widely among all cloven-hoofed animals within and between countries (Sellers, 1971; Donaldson et al., 2001; Mikkelsen et al., 2003). During the 2001 epidemic in the United Kingdom (UK) more than 2000 farms with approximately six million animals were culled. The total losses, composed of agriculture and food chain as well as compensation for slaughtered animals and clean-up costs, added up to £3.1 billion and £2.5 billion, respectively (Gloster et al., 2003). Current control measures were based on the eradication of infected animals, movement restrictions within designated areas and preventive culling of high risk contacts or of all farms within designated areas. Ethical discussions about culling of unaffected animals suggested vaccination or selective preventive culling as alternative control options. Actual control strategies should be evaluated concerning their feasibility. Furthermore, control measures should use limited resources as optimally as possible (Keeling, 2005).

Computer-based simulation models could be used to evaluate control strategies. Some recently developed models were a traditional SIR model for the FMD epidemic in the UK 2001 (Ferguson et al., 2001a,b) and a state transition model to identify high risk areas in France (Menach et al., 2005). Schoenbaum and Disney (2003) incorporated stochastic and economic elements in a state transition model to validate different mitigation strategies for the United States. Based on this model, Harvey et al. (2007) developed the North American Animal Disease Spread Model. Keeling (2005) described an increasing trend for the development of spatial-temporal simulations such as the Point-Pattern model of Gerbier et al. (2002) and the spatial stochastic epidemic model for three counties in California by Bates et al. (2003a,b). For the same region Kobayashi et al. (2007a,b) evaluated alternative FMD control strategies with a dynamic optimisation model. Karsten et al. (2005a,b) simulated the epidemiology and control of classical swine fever. They modelled stochastic elements using Monte-Carlo techniques. It is difficult to extrapolate experience of one country to another (Schoenbaum and Disney, 2003). Farm densities, farm sizes, and contact structures are different. Consequently, not only the output but also the simulation models themselves are rarely transferable without any loss of accuracy. The objective of the present study was to develop a spatial and temporal Monte-Carlo simulation model to describe the spread of FMDV in Northern Germany between farms

with cattle, pig or sheep. A farm consisted of sub-units defined by their type of livestock. Unlike existing models, personnel and vehicles moving from one farm to another were modelled as a routing problem. The virus did not spread randomly but started on an infectious farm following the route. In addition to other models (Bates et al., 2003a; Kobayashi et al., 2007a), the estimation of airborne spread by a Gaussian Dispersion model was integrated into the simulation model.

The present paper describes the simulation model. The sensitivity analysis of the model can be found in Traulsen et al. (2008). In further analysis, the influence of different control strategies will be evaluated and interactions with regional and structural distinctions estimated.

2 Material and Methods

The spatial and temporal Monte-Carlo simulation model simulated the spread of FMDV in a given region on a daily basis. The program was written in the object oriented language C++. Routines from the NAG C library (NAG, 2002) were used to generate random numbers. The statistical evaluation of the simulation output was carried out with the statistical program package SAS (SAS, 2003).

2.1 Farm data

Farms were structured in sub-units, characterised by their kind of livestock and their production type. Cattle units were subdivided into units of dairy cows, fattening bulls or mother cows, pig units into multipliers, farrowing or fattening units, while sheep units were not further subdivided. A farm comprised of one or several production units, which could be combined arbitrarily. Each farm was localised by x-/y-coordinates and the number of animals were assigned to each sub-unit. GIS-data could be processed in the model. The farm data in this analysis was derived from the Farm Structure Survey 2003 (Forschungsdatenzentrum, 2005). Every farm in Germany was asked about their livestock, employees, farm land, etc.. The data set for the simulation comprised the number of animals per species in each sub-unit in size classes and to which 'Gemeinde' (smallest administrative unit) the farm belonged. Within the administrative unit the farms were randomly distributed with the Hawth's Analysis Tool (Anonymous, 2006) for the Program ArcGIS 9.1 (ESRI, 2004). The class sizes were chosen according to the distribution of

the size of german farms (0-10, 10-50, 50-100, 100-500, 500-1000, 1000-2000, 2000-3000, 3000-4000, >4000 animals per unit).

2.2 Course of the disease

The course of the disease was the same for all species (shown in Figure 1) but the temporal development was different. Consequently, parameters such as the incubation period were species-specific (Alexandersen et al., 2003; Mahy, 2005). The range of the incubation periods varied between 4 and 14 days, estimated from previous epidemics (Mahy, 2005; Gloster et al., 1982; Donaldson, 1979; Donaldson et al., 1982b; Gloster et al., 2003) and was modelled with a log-normal distribution (Sartwell, 1950). The infected animals became infectious after a species-specific time period before the onset of clinical signs (Rivas et al., 2003). With the onset of symptoms, the animals could be identified as diseased and be diagnosed. Clinical disease was most obvious in pigs and cattle, while the sheep had rather mild lesions (Mahy, 2005; Ganter et al., 2001; French et al., 2002). Consequently, diseased pigs and cattle could be identified more easily and more quickly than sheep. The time periods for the different species are shown in Table 1.

Table 1: Infection parameters for cattle, pigs and sheep in days

	Cattle	Pigs	Sheep
start infectious (days post infection)	3	2	2
incubation period (mean of log-normal distribution)	8	8	10
delay diagnosis (days post onset of symptoms)	5	6	8

The implementation of control zones influenced the time until diagnosis and the time until culling, respectively. If control measures were present, people were more aware of FMD and diagnostic tests were applied. Consequently, infected animals were detected earlier. The control-zone-specific delay of diagnosis as well as delay of culling are shown in Table 4 in 2.4. In the simulation model, the delay of diagnosis respective culling was assumed to depend on both the species and the control measure. After confirmation of the FMDV infection in a sub-unit, certain control measures (described in 2.4) were established for all sub-units on the infected farm and surrounding farms. All sub-units on the infected farm were culled immediately the day after diagnosis. A repopulation of the sub-units was neglected.

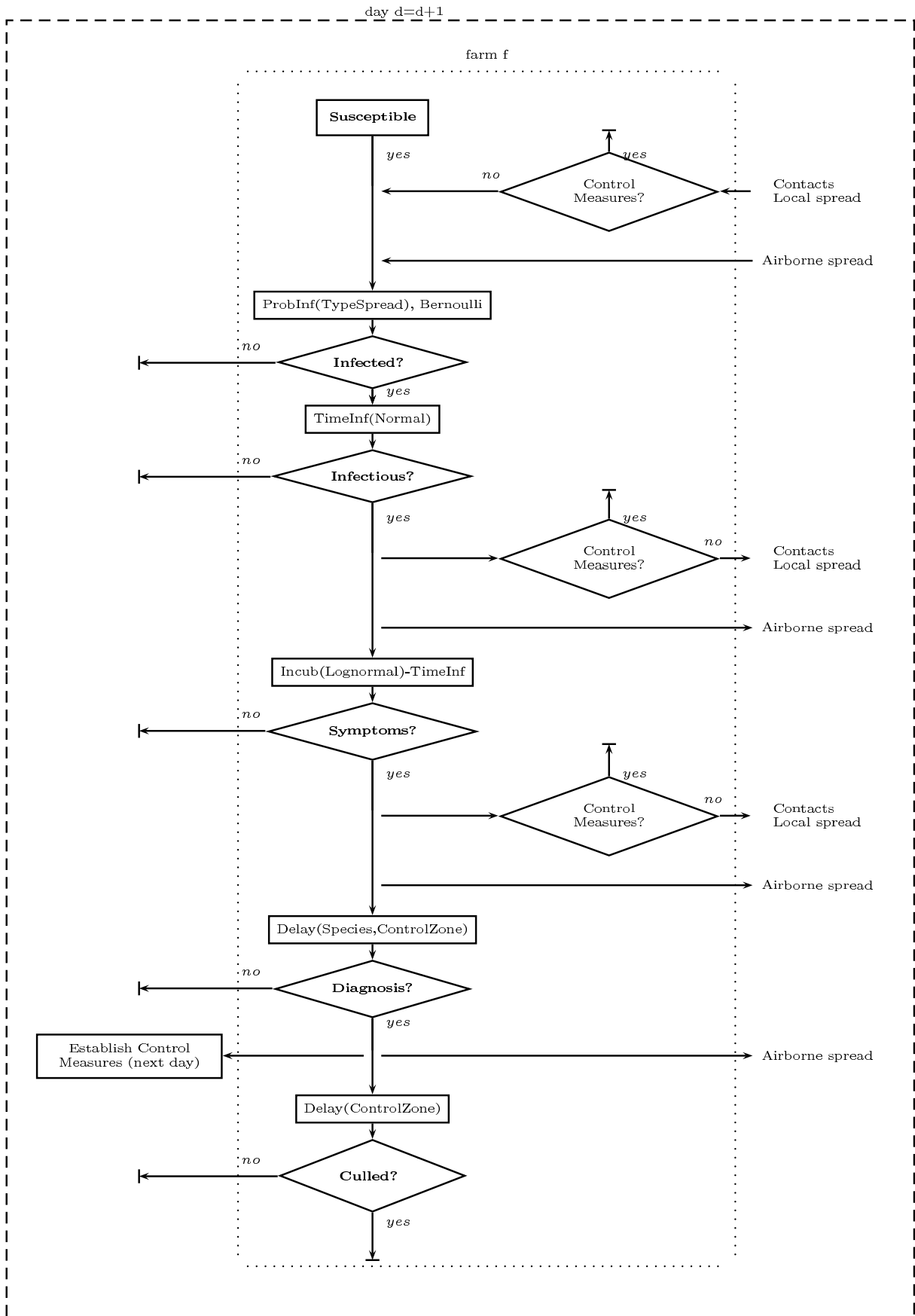


Figure 1: Exemplary process flow for the susceptible farm f on day t (simplified), ProbInf: infection probability, TimeInf: time from infection until infectious, Incub: incubation period

2.3 Virus transmission

The most common spread mechanism for FMDV is direct contact between infected and susceptible animals (Kitching et al., 2005). Furthermore, the virus can be spread indirectly via personnel and vehicles moving from one farm to another, via the air and locally (Donaldson et al., 2001).

Direct and indirect contacts

Transport of infected animals from one farm to another implicated a high risk of virus transmission (Donaldson et al., 2001; Kitching et al., 2005). The most important indirect contact types were the bulk milk tanker, and the veterinarian and animal feed vehicles, as these made regular visits to a lot of farms per day, often with direct animal contact. The number of farms being visited on a certain day was determined by the quotient of the total number of farms and the mean visiting interval. These farms were randomly chosen with a Poisson distribution ($\lambda = 1.2$) depending on the time period from the last visit. The longer this period was, the more likely was a visit on the actual day. Parameters describing the contact structure are shown in Table 2 and were quantified by a questionnaire among farms and dairies in Northern Germany (Witte, 2006).

Table 2: Mean visiting interval in days (interval), number of customers per route (customer) and transmission probability (a) for the different contact types (Witte, 2006)

	Direct contacts			Indirect contacts		
	Dairy	Farrowing	Multiplier	Vet ¹	Milk ²	Feed ³
interval	21	21	100	21	1	21
customer	1-3 ⁴	1-3 ⁴		10	20	15
a	0.5	0.5	0.05	0.3	0.15	0.15

¹: Veterinarian, ²: Bulk milk tanker, ³: Animal feed vehicle ⁴: uniform distribution

Routes for the indirect contacts started at a given depot, visited a certain number of farms and returned to the depot. The routes of the bulk milk tanker were constant during an epidemic while the routes for the veterinarian and animal feed vehicles were recalculated every day. An infectious farm could transmit the virus to its successors with decreasing probability *prob* modelled by an exponential function depending on the successors' position *pos* behind the infectious farm and the contact-specific transmission probability *a* (see Table 2):

$$prob = 0.05 + exp(ln(a) \times pos)$$

The distribution approximated asymptotically the minimal transmission probability (0.05). In the present simulation, the direct transport of calves from a dairy unit to a fattening unit, gilts from a multiplier to a farrowing unit and piglets from a farrowing unit to a fattening pig unit was implemented. If a dairy or farrowing unit and the accordant fattening unit were on the same farm, no animals were sold to other farms and this farm produced in a closed system. Farms without a fattening unit either sold all their animals directly to a certain number of fattening farms (contract distribution) or the animals were randomly distributed by a dealer to any other fattening farm (trade). Distribution via trade was more likely for dairy units compared to farrowing units 90% and 40% respectively. The remaining 10% respective 60% of each sub-unit sold their animals direct, following constant contracts. The routes of the bulk milk tanker were defined randomly at the beginning of the simulation. As infected dairy farms were not allowed to deliver milk, these were removed from the route but not replaced with another farm. The veterinarian visited all types of species while animal feed was delivered with separate vehicles to dairy, cattle fattening, mother cow, farrowing, finishing and sheep units.

Routing problem - the Nearest-Neighbour Algorithm

The procedure to determine the routes was the same for all contact types. The units visited on the actual day were assigned randomly to a certain route until the capacity of the route was fulfilled. Furthermore, the units of each route had to be put into a certain order. The route was determined to be the shortest visiting all units, as this was the most common optimisation criteria under economical and ecological aspects. The distance between two units was defined as the Euclidean distance calculated using the x-/y-coordinates. The routing problem was to find the shortest route consecutively visiting a given number of units. Routing problems were NP-hard (NP: Non-Deterministic Polynomial) and solving algorithms were requested to give optimal solutions in a reasonable amount of time. Exact algorithms were usable to solve this problem only for small numbers of units because the number of possible routes increased exponentially with the number of units to be visited. Therefore heuristics were used to give an approximating solution. One heuristic was the Nearest-Neighbour Algorithm that was simple and fast

(Grünert and Irnich, 2005).

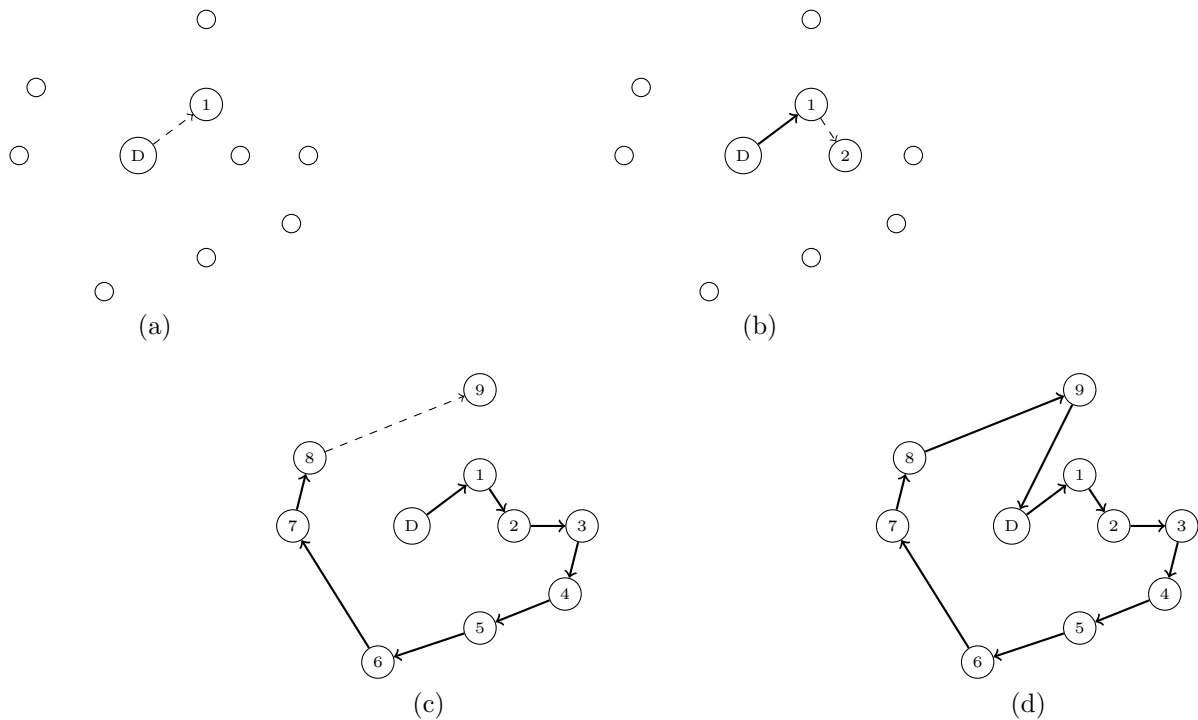


Figure 2: Example of using the Nearest-Neighbour Algorithm to find the shortest tour from one depot (D) through 9 farms presented in figures a-d

In the simulation model, the depot (D) was placed in the geographical centre of the region (see Figure 2). Starting the algorithm, the distance between the depot and all units was calculated and the unit with the shortest distance was chosen as the first stop (Figure 2 (a)). Now all the distances from this unit to all others were calculated and again the closest one was added to the route (Figure 2 (b)). This procedure was continued until the last unit had been integrated (Figure 2 (c)) and the route was completed with a direct return to the depot (Figure 2 (d)).

Airborne transmission

The airborne spread of FMDV was determined by the number and species of the animals on the source farm, the virus type, environmental conditions and the species and number of animals located downwind (Donaldson, 1979; Gloster and Alexandersen, 2004; Mahy, 2005; Gloster et al., 1981). FMDV was able to spread up to 60 km over land and 300 km over water (Donaldson et al., 1982a; Sørensen et al., 2000; Gloster et al., 2003). The maximal transport over long distances required a high virus output (pigs in acute stages), low virus dispersion, high virus survival and a large number of susceptible

livestock exposed to infected air for many hours (Gloster et al., 1982; Donaldson et al., 1982b). Advantageous weather conditions for airborne spread were a relative humidity of minimum 65-70% (Donaldson, 1979; Gloster et al., 2003, 2005), medium temperatures (Gloster et al., 2004), medium and lower wind speeds from a constant direction and stable atmospheric conditions (Gloster et al., 1982). At times of high precipitation the maximum transportation distance was reduced because of washing out. High wind speeds lead to more turbulence and the virus was transported over shorter distances. Sørensen et al. (2000) determined with a simulation model that one pig can infect a cow up to a distance of 5 km. The airborne spread of FMDV was modelled with a Gaussian Dispersion model, describing the spread of a virus plume within a 10 km distance around the source farm in the direction of the wind. Spreading within this circle was likely when dispersion occurred over land (Gloster, 1982; Moutou and Durand, 1994). For all farms matching these criteria the concentration of the virus \bar{c} in $TCID_{50}/m^3 \cdot day$ ($TCID_{50}$: 50% tissue culture infectious dose) was determined by the Gaussian Dispersion model:

$$\bar{c}(x, y, z) = \frac{Q}{2\pi\bar{u}\sigma_y\sigma_z} \exp\left(-\frac{y^2}{2\sigma_y^2}\right) \left[\exp\left(-\frac{(z-h)^2}{2\sigma_z^2}\right) + \exp\left(-\frac{(z+h)^2}{2\sigma_z^2}\right) \right]$$

$$\sigma_y = B\left(\frac{x}{\bar{u}}\right)^\beta, \sigma_z = A\left(\frac{x}{\bar{u}}\right)^\alpha$$

The concentration \bar{c} was calculated depending on the wind speed \bar{u} in m/s , the virus emission rate Q in $TCID_{50}/s$, the coordinates of the destination farm x, y, z and the virus emission high h in m . The source farm was located at the coordinates (0,0). The dispersion parameters σ_y and σ_z depended on the atmospheric stability parameters B, β, A and α defined in the ÖNORM 1992 (Anonymous, 1992).

Table 3: Quantities in $\log_{10}TCID_{50}virus/24h$ depending on the day of clinical disease and the species (Sørensen et al., 2000)

	Day of clinical disease						
	-2	-1	0	1	2	3	4
cattle			3.5	4.5	5.1	4.7	4.1
sheep	3.4	4.6	5.1	4.0	3.2	2.7	2.4
pigs			4.3	8.6	8.6	7.1	5.4

As shown in Table 3 cattle and pigs started emitting the airborne virus with the onset of clinical symptoms, while sheep started two days earlier (Sørensen et al., 2000).

Threshold concentrations for each species infecting one animal were 0.06 for cattle, 7.7 for pigs and $1.11 \text{ TCID}_{50}/\text{m}^3$ for sheep (Sørensen et al., 2000; Donaldson et al., 1982a). Estimated concentrations above the according threshold concentration resulted with increasing probability in an infection (Gloster, 1982; French et al., 2002). This was designed with an exponential probability function.

Local spread

Local spread summarises the virus transmission by rodents, cats and dogs that move from one farm to another. It was restricted to a distance up to 1000 m around an infectious farm. Three circles (≤ 250 m, 250-500 m, > 500 -1000 m) were defined with different infection probabilities 0.05, 0.02, 0.01, respectively. For the 2001 epidemic in the UK, Ferguson et al. (2001b) estimated that farms 0.5, 1 or 1.5 km away from an infected farm had infection probabilities of 0.26, 0.06 and 0.02, respectively.

2.4 Control options

According to the EU Directive (2003/85/EG) (Anonymous, 2003) and the German Regulation (Anonymous, 2004) different control measures were implemented in the simulation program (Table 4). Furthermore, each control option was defined by specific parameters: the size, the success of an emergency vaccination or contact tracing, the days until a farm was diagnosed or culled, etc..

Table 4: Parameters for control measures according to the EU Directive (2003/85/EG)

Control measure	Circle/ Time period	Delay diagnosis (days) ¹	Delay culling (days) ²
no control option		8	3
temporary control zone	0-1 km	7	2
protection zone	0-3 km	4	1
surveillance zone	3-10 km	4	1
preventive culling zone	0-1 km	2	1
vaccination zone (vaccine 1)	0-1 km	1	1
vaccination zone (vaccine 2)	1-5 km	1	2
contact tracing (for-, backward)	last 3 weeks	1	1

¹: delay of diagnosis after the onset of clinical symptoms

²: delay of culling after the diagnosis

Before the confirmation of FMD, a temporary control zone could be established around the suspicious farm if this was located in a high-risk area. Neither animal movements nor personal and vehicle contacts were allowed. People within this zone were aware of FMD so that the detection probability of an infected farm increased. As shown in Table 4, it was assumed that the delay of diagnosis after the onset of symptoms decreased from 8 to 7 days, while the delay of culling after diagnosis reduced from 3 to 2 days. After confirmation of the presence of FMDV, a protection zone and a surveillance zone were established based on a minimum radius of 3 respective 10 km centered on the infected farm. Within seven days all farms were screened for FMDV. All contacts within the last 21 days were traced backwards and forwards and movement restrictions were established. The delay of diagnosis and culling was reduced to 4 and 1, respectively (see Table 4). Preventive culling zones around infected farms were established in regions with a high farm density. All susceptible animals within this zone were culled to inhibit virus transmission by reducing the number of susceptible animals. The size of the zone depended on the animal density within the region and usually varied between 250 m and 1000 m. A further control measure was the emergency vaccination. Since 1991 regular preventive vaccinations against FMD have been prohibited in the EU (Visser and Thiel, 2001; Anonymous, 2003). But in case of an outbreak it was possible to carry out an emergency vaccination. The vaccination could not start immediately after confirmation of FMDV because an emergency vaccination plan had to be approved by the EU Commission. In the present model, it was possible to define two different vaccination zones, differing in size and vaccine type. Contact tracing was an additional control measure and carried out backwards and forwards within a specified time period (for example, the last 21 days). Based on the diagnosed farm, forward tracing identified all farms it had contacts with, while backward tracing identified all farms it had contacts from. The success of contact tracing depended on the point in time the contact took place. With every week since the contact had taken place, the mean probability of a successful tracing μ_{trac} decreased by 10 %. For each contact the specific success was determined by drawing a random number from a normal distribution with the mean μ_{trac} . If a second random number from a uniform distribution (0, 1) was below the specific success, the contact was traced successfully and the defined control option (movement restrictions, preventive culling or vaccination) was established on the traced farm. The control option was defined by the user and depended on the farm density in the region and the risk of further spread emanating from this farm.

2.5 Example

An example with two scenarios (with and without airborne spread) was simulated. A region with 729 farms was chosen, consisting of 462 dairy cow units, 412 fattening bull units, 165 mother cow units, 79 sheep units, 49 farrowing units and 59 fattening pig units and a density of $1.05 \text{ farms}/\text{km}^2$. 250 simulation runs per scenario were performed. The index case was localised on a dairy farm in the centre of the region. The establishment of protection and surveillance zones and preventive culling within 1 km around an infected farm was assumed. The results of the model were presented with the mean epidemic duration in days, the mean number of infected and culled farms.

3 Results

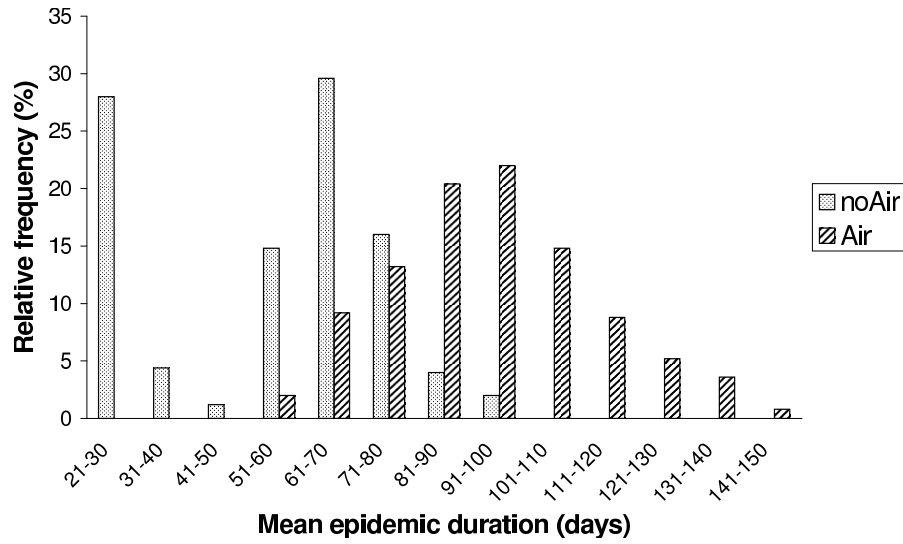
In Table 5 the mean, median, minimum and maximum for the output variables mean epidemic duration (days), and mean number of infected and culled farms is shown depending on airborne spread.

Table 5: Mean, median, minimum (*Min*), and maximum (*Max*) for the response variables mean epidemic duration in days, mean number infected and culled farms depending on airborne spread (*Air*)

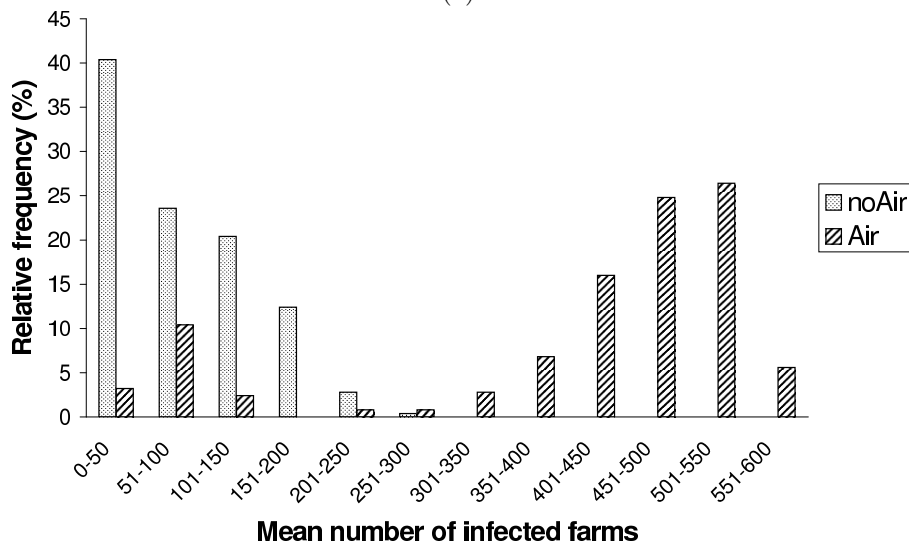
Air	Response variable	<i>Mean</i>	<i>Median</i>	<i>Min</i>	<i>Max</i>
no	duration	52.9	61.5	21.0	98.0
no	infected farms	74.0	73.5	1.0	269.0
no	culled farms	168.6	195.5	4.0	445.0
yes	duration	94.1	93.0	56.0	147.0
yes	infected farms	406.7	465.5	42.0	588.0
yes	culled farms	543.0	623.0	94.0	693.0

With airborne spread, more farms were infected and culled on average than without 168.6 vs. 543.0 and 74.0 vs. 406.7, respectively. The wide range within the response variables indicate the high difference between the largest and the smallest epidemics. Without airborne spread, the mean and the median differed for the epidemic duration and the number of culled farms. In contrast with airborne spread the differences could be observed for the number of infected and culled farms. The difference between the mean and the median indicated that the data were not normally distributed.

In Figure 3 the distribution of the mean epidemic duration and the mean number of



(a)



(b)

Figure 3: Relative frequency (%) of the mean epidemic duration (days) and mean number of infected farms in classes of 10 or 50, respectively, depending on airborne spread

infected farms is shown depending on the presence of airborne spread. Neglecting airborne spread resulted in a two peaked distribution of the epidemic duration. Nearly 30% of the epidemics were over after 30 days. The other epidemics lasted longer with a peak around the 61-70 days class. Adding airborne spread, the distribution resembled more a normal distribution with its mean at the 90-100 days class. The mean number of infected farms was divided into classes of 50. Without airborne spread, the distribution was right skewed indicating that a large epidemic size was unlikely. Adding airborne spread reduced the number of small epidemics, larger epidemics became more likely and the maximal size increased. The distribution was left skewed.

4 Discussion

4.1 Farm data

In the present model, farms were localised at a point with x-/y-coordinates, neglecting the fact that in reality farms were more an area than a point. Nevertheless, spatial distribution as well as Euclidean distances between farms were incorporated and therefore spatial-specific control strategies could be determined. Savill et al. (2006) concluded in an analysis of the 2001 FMD epidemic in the UK that a simple spatial kernel based on the Euclidean distance was sufficient for most regions.

In most models, the type of a farm with different livestock was determined by the dominant species while the other species were neglected. In the model of Bates et al. (2003a) a certain number of different farm types were defined by their livestock and size. Harvey et al. (2007) distinguished production units with different livestock, size and transition states. In the present model, the arbitrary combination of livestock within one farm was possible. The infection chain and virus transmission was treated separately for each livestock.

4.2 Virus transmission

Virus transmission at a regional level was estimated instead of local virus dispersion. Consequently, within-farm spread was not included. Special models have been developed to estimate within-farm spread (Carpenter et al., 2004). Bates et al. (2003a,b) estimated the within-farm spread using a deterministic Reed-Frost model and found out that it took

4 days for swine, 9 days for dairy herds, 10 days for sheep and beef herds with less than 250 animals. The spreading time depended on the reproduction time of the virus within the animals and consequently on their age and immune state. Additionally, differences in housing would have to be taken into account, because Bouma et al. (2004) found that no FMDV transmission occurred between individually housed calves. In the present mode, the ranges of the incubation periods were integrated with a log-normal distribution. Nevertheless, the virus transmission within the farm might be overestimated.

The representation of the contacts between farms as a routing problem was more realistic than the random selection of a contact destination. Farms that followed an infectious farm on a periodical route, such as the route of the bulk milk tanker, had a higher risk of infection than others. Further development in the representation of the contact structure between farms should take the road structure into account. Rivas et al. (2003) found a significant impact of the road density on the course of an epidemic, especially in the early stages of an epidemic.

The assumption that farms removed from the routes of the bulk milk tanker were not replaced seemed realistic. Perhaps, in long-term epidemics with a high number of infected dairy units, routes would be adapted. In the present model virus transmission via milk was possible from the day the animals became infectious up to their culling. The results of Thurmond and Perez (2006), Tomasula and Konstance (2004) and Burrows (1968) showed that shedding of the virus did not start immediately after infection and the amount changed over time. Consequently, the spread via bulk milk tanker might be overestimated.

Models for airborne spread of FMDV based on Gaussian Dispersion were widespread and established in epidemiology. Several models for short- and long-range transmission were developed by Gloster et al. (1982, 2003) and Sørensen et al. (2000, 2001). However, only Harvey et al. (2007) incorporated airborne spread into their model. They modelled airborne spread up to 1 km, although it was likely up to 10 km (Gloster, 1982). Recently Lagrangian particle models were used to estimate the airborne spread of FMDV (Mayer et al., 2007). In contrast to Gaussian Dispersion models, topography and time-variant meteorological conditions were to be taken into account. Due to the complexity of the Lagrangian model itself and its input parameters a Gaussian Dispersion model was preferred.

4.3 Control options

In the present simulation, control options could be combined arbitrarily but were constant for each scenario. Kobayashi et al. (2007a,b) suggested that the optimal control strategy changed during an epidemic. In the early stages of an FMD outbreak, aggressive depopulation might be most effective while in later phases strategies with vaccination were most preferable. However, they did not describe optimal stage-specific control strategies. Furthermore, an interaction between the stage of the epidemic and the optimal control measure might be possible. Rivas et al. (2003) found interactions between the farm size and the optimal control strategy. Large farms tended to be affected in the early stages of an epidemic, while later small farms were at higher risk. To adapt the control measure during an epidemic high personal and logistical effort is required and economic and welfare consequences have to be taken into account.

In the present simulation model, movement restrictions were strictly followed. In contrast, experts consulted by Bates et al. (2003a) estimated that in case of an FMD outbreak 5% and 12% of the livestock movements prior to the epidemic continued within the infected area and surveillance zone, respectively. Furthermore, they presented a study from the Netherlands illustrating that illegal livestock movements might have contributed to delays in eradicating classical swine fever. Karsten et al. (2007) showed that changes in the effectiveness of contact tracing influenced the success of disease eradication. However, in the present model control measures could be established with delay and the variation of the success of contact tracing and emergency vaccination was incorporated.

4.4 Example

In the present study, no response variable followed a normal distribution except the mean epidemic duration assuming airborne transmission. In contrast, each variable showed a different distribution. Including airborne spread, the distributions of both response variables shifted to the right. More farms were affected and the epidemic lasted longer. The two peaked distribution of the mean epidemic duration neglecting airborne spread reflected two types of epidemics: epidemics limited to the index farm and a small number of further cases (first peak) and the wide spread of the virus by secondary infections (second peak).

5 Conclusion

The developed spatial and temporal Monte-Carlo simulation model can be used to describe the epidemiology and control of FMD epidemics. The virus could be spread via direct and indirect contacts, locally and via the air. Animal distribution was described by contract selling or trade. Indirect contacts between farms were modelled as a routing problem instead of random selection. Airborne spread was integrated using in a Gaussian Dispersion model. Current control measures including preventive culling, contact tracing and emergency vaccination were implemented. Results of an example indicated that the chosen response variables were not normally distributed. Statistical analysis of the simulation output would have to take the different distributions into account.

Acknowledgements

We thank J. Teuffert for the helpful discussions, M. Elouali for the assistance with the Nearest-Neighbour Algorithm and furthermore F. Rubel and D. Mayer for concrete statements about the use and applicability of atmospheric dispersion models.

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Chapter 2:

A spatial and temporal Monte-Carlo simulation model of foot and mouth disease epidemics: II. Validation of the model

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Abstract

A sensitivity analysis with a fractional factorial design was used to validate a spatial and temporal Monte-Carlo simulation model for foot and mouth disease. The virus could spread via the air and via direct and indirect contacts between farms. Animals were distributed directly via contract selling or randomly via trade. Indirect contacts were presented by routes of the veterinarian, the animal feed vehicle and the bulk milk tanker. In the validation model four basic factors were included: airborne spread, incubation period, time from infection until infectivity and time from the onset of symptoms until diagnosis. These were combined with additional factors in three different models. Model A comprised additionally the farm density and the type of the index case, Model B the length of the routes of the veterinarian, animal feed vehicle and bulk milk tanker as well as the visiting interval and the type of the distribution of animals, and Model C the control strategy and its delay of establishment. The influence of the main factors as well as two-factor interactions were estimated in linear models assuming a negative binomial distribution. The epidemic duration and the number of infected and culled farms were chosen as response variables. The main effects as well as certain interactions showed a significant impact on the response variables. Particularly, the airborne spread significantly influenced the course of the epidemic and interacted with all main factors. The simulation model could be used to describe foot and mouth disease epidemics under the given assumptions.

Keywords: Foot and mouth disease, Validation, Fractional factorial design, Sensitivity analysis

1 Introduction

Validation of simulation models is an important issue to ensure that the results of these models conform to reality. In general, simulation models are developed for a special purpose or problem and its validity is determined with respect to that purpose. Consequently, the model would be valid for one set of experimental conditions but not transferable to another. Before the validation of a simulation model the range of application and the required amount of accuracy have to be defined (Sargent, 2003; Law and Kelton, 1982).

The realisation of the validation depended on the data availability (Kleijnen, 1999). For the validation of an animal disease simulation model real data were rare. However, qualitative expert knowledge still exists. Kleijnen (1999) recommended a sensitivity analysis to investigate the reaction of the simulation model to changes in the input parameters or the structure of the model. When the outcome was not conform to expert knowledge, there were programming or conceptual errors in the model. A various number of input factors influenced the epidemiology and control of an animal disease. The number of scenarios to be simulated grew exponentially with the number of factors to examine. A possible solution was to apply a fractional factorial design described by Box and Hunter (1961a,b). Karsten et al. (2005) used a sensitivity analysis with a 2^{7-2} fractional factorial design to validate a Monte-Carlo simulation model of classical swine fever epidemics.

Traulsen et al. (2008) developed a spatial and temporal Monte-Carlo simulation model to describe foot and mouth disease (FMD) spread within a certain region. Several control measures and spread mechanisms were incorporated and represented by probability distributions to consider the stochastic process of the virus spread.

The objective of the present study was to validate the FMD simulation model using a sensitivity analysis with a fractional factorial design.

2 Material and Methods

2.1 Description of the simulation model

A spatial and temporal Monte-Carlo simulation model was developed to describe the spread of foot and mouth disease virus (FMDV) in a given region on a daily basis. Each farm consisted of different sub-units representing different livestock and was located by

its x-/y-coordinates. The epidemic started with the infection of the index case and could spread via the air and via direct and indirect contacts. The course of an infection was modelled with the infection states susceptible, infected, infectious, symptoms, diagnosed and culled. Animals could be distributed directly by contract selling or randomly by trade. Indirect contacts were modelled as a routing problem. Routes for the veterinarian, animal feed vehicle and bulk milk tanker were solved with the Nearest-Neighbour Algorithm. Control strategies to eradicate an epidemic were implemented according to the EU Directive (2003/85/EG) (Anonymous, 2003): an infected farm was culled immediately and different control measures such as the establishment of protection and surveillance zones, preventive culling or emergency vaccination could be implemented in defined circles around the infected farm. A detailed description of the simulation model and the input parameters was given by Traulsen et al. (2008).

2.2 Farm data

The farm data was derived from the Farm Structure Survey 2003 (Forschungsdatenzentrum, 2005). Every farm in Germany was asked about their livestock, employees, farm land, etc.. The data set for the simulation comprised the number of animals per species on each farm in size classes and to which 'Gemeinde' (smallest administrative unit) the farm belonged. Within the administrative unit the farm was randomly distributed with the Hawth's Analysis Tool (Anonymous, 2006) for the Program ArcGIS 9.1 (ESRI, 2004). In the present study a region with 729 farms was chosen. The farms consisted of 462 dairy cow sub-units, 412 fattening bull sub-units, 165 mother cow sub-units, 79 sheep sub-units, 49 farrowing sub-units and 59 fattening pig sub-units.

2.3 Fractional factorial design

Many factors had an influence on the output of the simulation model. For a full design of these factors many scenarios had to be simulated. In a fractional factorial design, a certain fraction of the full model was used but all factors of the full model were estimated (Box and Hunter, 1961a,b). Assuming that higher-order interactions between main factors were negligible these were used to estimate other main factors. Kleijnen (1999) recommended a 2^{k-p} fractional factorial design, while 2 was the number of factor levels, k was the number of factors varied during the experiment and p was the extent of frac-

tionation. To construct a 2^{k-p} fractional factorial design a full 2^k design was assumed and the missing p factors were estimated by combinations of the other factors (higher-order interactions). The missing factors are confounded with the respective interaction. Assuming that higher-order interactions are negligible the missing factor can nevertheless be estimated. The degree to which the estimated main factors were confounded with the estimated interactions was described by the resolution of the model. In a design of resolution four no main effects were confounded with another main factor or two-factor interaction. Furthermore, two-factor interactions were partially confounded with each other. A resolution of six meant that main effects were confounded with five-factor interactions and two-factor interactions were confounded with four-factor interactions (Box and Hunter, 1961a,b; Montgomery, 2005).

2.4 Scenarios

In the present study eleven factors were analysed in three different models. Parameters describing the characteristics of the virus type were chosen for the basic model: airborne spread, incubation period, time from infection until infectivity and time from the onset of symptoms until diagnosis. Different additional factors important for virus spread describing regional and structural differences as well as control options were combined with the basic factors. In Model A, factors describing the regional situation (farm density, type of index farm) were added. Model B took factors according to the disease spread by contacts (farms per route, visiting interval, proportion of contract selling to trade) into account. In Model C, factors describing the control measures (delay of the establishment of control measures, control strategy) were analysed. Model A and C had six factors each and a 2^{6-1} fractional-factorial design of resolution six was applied. A 2^{7-2} design with resolution four was defined for the seven factors of Model B. The study comprised 32 scenarios for each of the models and each scenario was repeated 100 times.

Table 1 shows the values for the two levels (low and high) assumed for each factor. The levels describe the range of each parameter the model should be applicable for. The ranges of each basic parameter represented the variability of different virus types (Mahy, 2005; Gloster et al., 1982; Donaldson, 1979; Donaldson et al., 1982; Gloster et al., 2003). The farm densities described mean densities in Northern Germany. The different index types differ in their contact structure: fattening farms had fewer animal, vehicle and personnel contacts than dairy farms. Consequently, different courses of the epidemics were expected.

Table 1: Factors and their levels in the fractional factorial designs

Model	Factor	Low value(s)	High value(s)	
basic	(<i>air</i>)	airborne spread	no	yes
	(<i>inc</i>)	incubation period (<i>days</i>) ¹	8, 8, 10	10, 10, 12
	(<i>inf</i>)	time from infection until infectivity (<i>days</i>) ¹	3, 2, 3	4, 3, 4
	(<i>diag</i>)	time from symptoms until diagnosis (<i>days</i>) ¹	5, 6, 8	7, 8, 11
A	(<i>den</i>)	farm density (<i>farms/km</i> ²)	0.67	1.05
	(<i>ind</i>)	type index farm	fatt bulls ⁴	dairy cows
B	(<i>route</i>)	farms per route ²	7, 10, 15	10, 15, 22
	(<i>int</i>)	visiting interval (<i>days</i>) ²	14, 14, 1	21, 21, 1
	(<i>prop</i>)	proportion of trade to contract selling ³	0.5, 0.2	0.9, 0.4
C	(<i>del</i>)	delay control measures (<i>days</i>)	1	3
	(<i>cont</i>)	control strategy ⁵	P+S	P+S+PC+CT

¹: for cattle, pigs, sheep

²: for the veterinarian, animal feed vehicle, bulk milk tanker

³: for a dairy farm, farrowing farm

⁴: fattening bull farm

⁵: P: protection zone (0-3 km), S: surveillance zone (>3-10 km), PC: preventive culling (< 1 km), CT: contact tracing (last 3 weeks)

A questionnaire among farms in Northern Germany (Witte, 2006) determined the levels of the additional parameters in Model B. Control strategies were chosen according to the EU Directive (2003/85/EG) (Anonymous, 2003).

2.5 Statistical analysis

The FMD epidemics were described by three different response variables: the mean epidemic duration in days and the mean number of infected and culled farms. As these were measured as counts a negative binomial distribution was a better assumption for the description than a normal distribution. A linear model with a negative binomial distribution and a log link function was fitted to the data using the GENMOD procedure of the SAS program package (SAS, 2003).

Each linear model included the overall mean. The model for the 2^{6-1} fractional-factorial designs estimated all six main factors and all 15 two-factor interactions. The model for

the 2^{7-2} design included three pairs of confounded factors, so that besides all seven main effects only the following interactions were included:

Model B:

$$\begin{aligned}
\log(E(Y_{ijklpq})) = & \beta_0 + air_i + inc_j + inf_k + diag_l + route_o + int_p + prop_q \\
& +(air \times inc)_{ij} + (air \times inf)_{ik} + (air \times diag)_{il} \\
& +(air \times route)_{io} + (air \times int)_{ip} + (air \times prop)_{iq} \\
& +(inc \times inf)_{jk} + (inc \times diag)_{jl} \\
& +(inc \times route)_{jo} + (inc \times int)_{jp} + (inc \times prop)_{jq} \\
& +(inf \times diag)_{kl} + (inf \times route)_{ko} + (inf \times int)_{kp} \\
& +(inf \times prop)_{kq} + (diag \times route)_{lo} \\
& +(diag \times int)_{lp} + (diag \times prop)_{lq} + (route \times int)_{op} \\
& +(route \times prop)_{oq} + (int \times prop)_{pq}
\end{aligned}$$

where $E(Y_{ijklpq})$ was the expected value of the response variable, β_0 was the overall mean, air_i was the airborne spread, inc_j was the incubation period, inf_k was the time from infection until infectivity, $diag_l$ was the time from the onset of symptoms until diagnosis, $route_o$ was the number of farms on a route of the veterinarian, bulk milk tanker, etc., int_p was the visiting interval, $prop_q$ was the proportion of selling animals via trade compared to direct delivery, $(inc \times inf)_{ij}$ was the interaction between incubation period and time between infection and infectivity and so on. The interactions $inf \times route$ and $int \times prop$, $route \times prop$ and $inf \times int$ as well as $route \times int$ and $inf \times prop$ were confounded in pairs. The deviance of the response variables ranged from 1.03 to 1.20 and indicated that the models assumed fitted to the data. Least square means (LSM) were estimated on log scale. The significance was tested using Type III likelihood ratio statistics. The general direction of the factors was determined by linear contrast estimates.

3 Results

The significances of the main factors and two-level interactions for the response variables are shown in Table 2. Table 3 presents the estimated contrast co-efficients (differences between the LSMs on log scale) and their standard errors of the main factors for the

response variables. For Models A and B the mean number of culled farms is not shown. It was identical to the mean number of infected farms as only all infected farms were culled.

Basic factors

The tendencies of the four basic factors were consistent for all three models (Table 2). The high level of airborne spread, incubation period and time from symptoms until diagnosis resulted in a significantly higher mean epidemic duration as well as more infected and culled farms. Increasing the time from infection until infectivity decreased all response variables. The significance of the interactions between the basic factors differed between the models. Airborne spread showed significant interactions with all other factors.

Model A

In Model A the farm density and the type of the index case significantly influenced the response variables. A high farm density or a dairy farm as index case resulted in a higher mean epidemic duration and mean number of infected farms. The two levels of the farm density showed higher differences for the epidemic duration and size than the levels of the index type (1.09 and 3.7 vs. 0.08 and 0.31 in Table 3). Both additional factors interacted significantly with the basic factors airborne spread, time from infection until infectivity and time from symptoms until diagnosis (Table 2). The significant interaction $air \times den$ showed that the differences of the mean number of infected farms between the two farm density levels were higher with airborne spread than without (Figure 1 (a)). The mean number of infected farms increased more for the high density than for the low density. The significant interaction between the time from the onset of symptoms until the diagnosis and the index type indicated that with an increased time period the differences between the index types decreased. The increase in the mean number of infected farms was smaller for the dairy farm as index herd than the fattening bull farm (Figure 1 (b)). Furthermore, the farm density significantly interacted with the index type. The differences between the two density levels was higher for the dairy farm as index case than for the fattening bull farm (Figure 1 (c)).

Model B

In Model B only the number of farms visited per route showed a significant influence on the mean number of infected farms. The longer the route was, the more farms were

Table 2: Significances of the main factors and two-level interactions for the mean epidemic duration in days (dur) and mean number of infected (infec) and culled (cull) farms

Factor	Model A		Model B		Model C		
	dur	infec	dur	infec	dur	infec	cull
main factors							
<i>air</i>	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>inc</i>	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0003	0.0014
<i>inf</i>	0.0196	<0.0001	0.8048	<0.0001	0.7590	<0.0001	<0.0001
<i>diag</i>	0.0028	<0.0001	0.0339	<0.0001	0.0156	<0.0001	0.0002
<i>den</i>	<0.0001	<0.0001					
<i>ind</i>	<0.0001	<0.0001					
<i>route</i>			0.5409	<0.0001			
<i>int</i>			0.8936	0.8466			
<i>prop</i>			0.5060	0.7052			
<i>del</i>					<0.0001	<0.0001	<0.0001
<i>cont</i>					<0.0001	<0.0001	0.0049
two-level interactions							
<i>air</i> × <i>inc</i>	0.4539	0.2399	0.0965	0.3522	0.9347	0.6145	0.4989
<i>air</i> × <i>inf</i>	0.7895	0.0215	0.0037	0.0082	0.2863	0.1139	0.1321
<i>air</i> × <i>diag</i>	0.4933	0.1940	0.0069	0.1213	0.1153	0.7158	0.7974
<i>inc</i> × <i>inf</i>	0.0780	0.9432	0.7419	0.6786	0.4097	0.7606	0.7789
<i>air</i> × <i>ind</i>	0.0904	0.1644					
<i>air</i> × <i>den</i>	<0.0001	<0.0001					
<i>inf</i> × <i>ind</i>	0.0656	0.6998					
<i>inf</i> × <i>den</i>	0.4539	0.0962					
<i>diag</i> × <i>ind</i>	0.0957	0.0688					
<i>diag</i> × <i>den</i>	0.5013	0.0457					
<i>ind</i> × <i>den</i>	<0.0001	<0.0001					
<i>air</i> × <i>route</i>			0.4470	0.0108			
<i>air</i> × <i>cont</i>					0.0769	<0.0001	0.4816
<i>del</i> × <i>cont</i>					<0.0001	0.0999	<0.0001

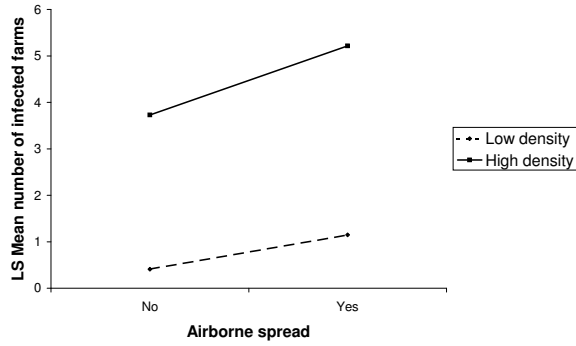
Table 3: Estimated contrast co-efficients (differences between the least square means on log scale) and standard error (*stdErr*) of the main factors for the mean epidemic duration in days (*dur*) and the mean number of infected (*infec*) and culled (*cull*) farms

Factor	Model A		Model B		Model C		
	<i>dur</i>	<i>infec</i>	<i>dur</i>	<i>infec</i>	<i>dur</i>	<i>infec</i>	<i>cull</i>
<i>air</i>	0.48	1.11	0.53	1.49	0.53	1.21	1.07
<i>inc</i>	0.12	0.30	0.10	0.19	0.10	0.17	0.14
<i>inf</i>	-0.05	-0.30	-0.01	-0.30	-0.01	-0.31	-0.26
<i>diag</i>	0.06	0.27	0.04	0.21	0.05	0.20	0.16
<i>den</i>	1.09	3.70					
<i>ind</i>	0.08	0.31					
<i>route</i>			0.01	0.30			
<i>int</i>			0.00	-0.01			
<i>prop</i>			0.01	0.02			
<i>del</i>					0.18	0.54	0.40
<i>cont</i>					-0.20	-0.39	0.12
<i>stdErr</i>	0.02	0.05	0.02	0.05	0.02	0.05	0.04

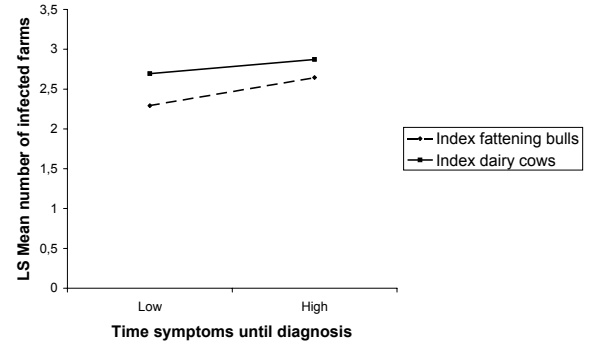
infected (difference of 0.3 of the LSMs on log scale in Table 3). Moreover, the number of farms per route showed a significant interaction with the airborne spread (Figure 1 (d)). Adding airborne spread the difference of the mean number of infected farms between the two farm density levels decreased.

Model C

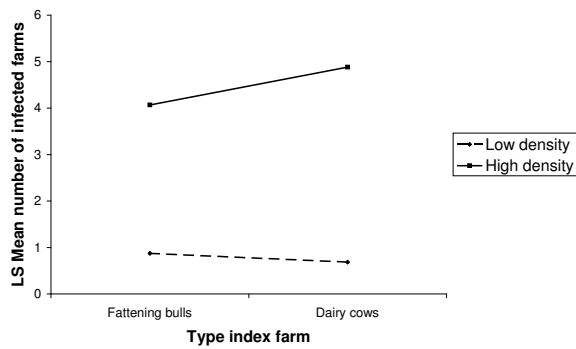
Both additional factors in Model C, i.e. the delay of the establishment of control measures and the control strategy, were highly significant. The later the control measures were established, the higher the mean epidemic duration and the mean number of infected and culled farms. Control strategies adding preventive culling and contact tracing resulted in shorter epidemics and fewer infected farms, but a higher number of culled farms (see Table 3). The control strategy showed a significant interaction with the airborne spread. Furthermore, the delay of establishment interacted significantly with the control strategy for all response variables (Table 2). The higher the delay of establishment was, the smaller the difference of the mean number of infected farms between the two control strategies (Figure 1 (e)). The same could be found for the mean number of culled farms in Figure 1 (f), but with smaller differences.



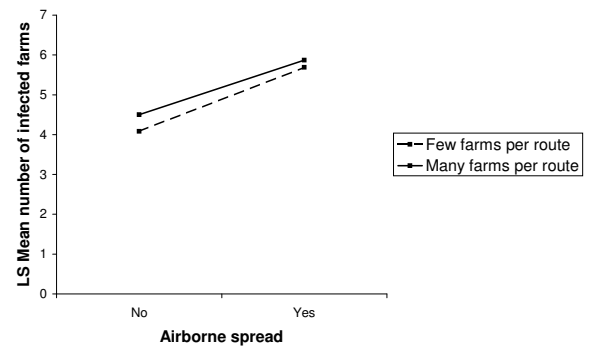
(a) $air \times den$, Model A



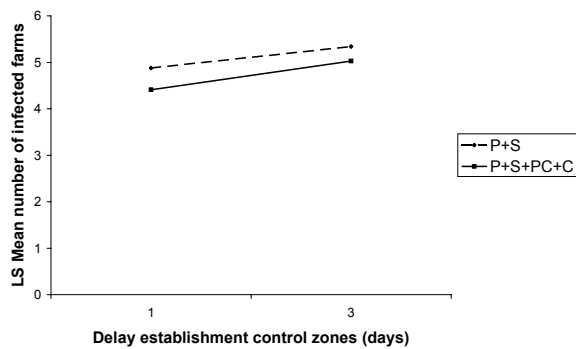
(b) $diag \times ind$, Model A



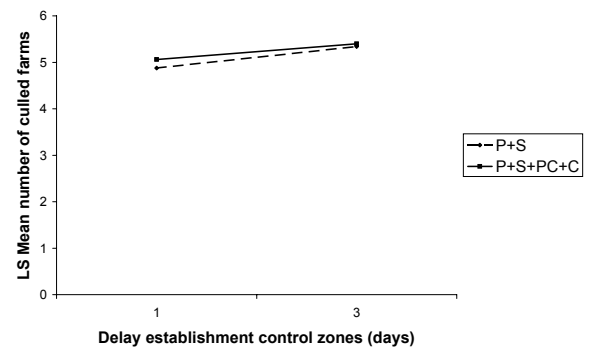
(c) $ind \times den$, Model A



(d) $air \times route$, Model B



(e) $del \times cont$, Model C



(f) $del \times cont$, Model C

Figure 1: Selected significant two-factor interactions (LS-Means on log scale)

4 Discussion

Fractional factorial designs were a useful tool to analyse many factors with optimal use of limited resources. Two-factor interactions known not to be present should be taken into account for the confounded factors, to have the maximal benefit from the design. Dividing the estimated factors into different models reduced the number of scenarios to be simulated (in total 96) but interactions between the additional factors could not be estimated. To estimate 11 factors in a single fractional factorial design without confounding between main effects and two-factor interactions would have resulted in a minimum of 128 scenarios (2^{11-4} design of resolution 5). Calculation capacity restricted the validation to 96 scenarios. However, interactions between the additional factors could be expected and have to be taken into account in further analysis, e.g. determination of optimal control strategies.

Basic factors

As expected, the outcome of the simulation model showed that larger epidemics were likely assuming airborne spread, a higher incubation period, a longer time from the onset of clinical symptoms to diagnosis or a shorter time from infection until infectivity. The time from infection until infectivity was per definition a part of the incubation period. A longer incubation period as well as a shorter time from infection until infectivity resulted in more infected farms because the virus could spread for a longer time period. The significant interaction between these factors in Model A showed that with longer incubation periods the mean number of infected farms increased more when the time until infectivity was shorter.

The time period from the onset of symptoms until the diagnosis depended on biological parameters of the virus type and in contrast to the other basic factors, additionally on the established control measures. If control measures were established, a diagnosis was more likely as people were more aware and animals were to be screened. All basic parameters except airborne spread were varied for cattle, pigs and sheep simultaneously. Keeling et al. (2001) and Menach et al. (2005) found that parameters related to sheep had a lower impact compared to cow parameters. Consequently, the observed impact of the incubation period could be due to an enlargement of the incubation period of cattle and pigs only. Probably, it would not make a difference changing the incubation period of the

sheep. The region in the present study consisted of much more cattle and pig sub-units than sheep, but in regions with almost only sheep it was likely that increasing incubation periods of sheep would nevertheless have an impact on the course of an epidemic.

Interactions between airborne spread and the additional factors indicated that in case of airborne transmission the spread of the virus was different and control measures had to be adapted. Virus types differ in their ability to be spread by air, e.g. the Type O UK 2001 strain, which was unlikely to spread more than 20 km by wind even with favourable weather conditions, while the C Noville strain had the potential to spread up to 300 km (Alexandersen et al., 2003). Consequently, in case of an outbreak, a fast identification of the virus type is necessary to establish the optimal control measures immediately. In the present study, favourable weather conditions for airborne spread with medium wind speed, stable atmospheric conditions and wind direction were assumed. The estimated influence of airborne spread could be regarded as an upper estimation but it was nevertheless a realistic assumption.

Model A

In the present analysis, the results for the regional factors were conform to simulations from Bates et al. (2003) and Kobayashi et al. (2007a,b). Dairy herds as index cases resulted in larger epidemics than fattening bull farms. Compared to fattening farms dairy farms had more contacts concerning the distribution of animals or the daily visit of the bulk milk tanker. Kobayashi et al. (2007a,b) determined in a simulation of FMDV spread in the USA that dairy herds should be given preferential attention in allocating control measures especially if these are limited. However, the pattern of the optimal control strategy did not vary between the types of the index case. Conform to expectations, an epidemic lasted longer and more farms were infected in densely populated areas (Morris et al., 2001; Rivas et al., 2003; Gerbier et al., 2001, 2002). The interaction between the farm density and the index case indicated that the differences in the epidemic duration between the densities was larger for epidemics starting in a dairy herd. Consequently, the allocation of control measures to dairy herds was even more important in densely than in sparsely populated regions.

Model B

As expected the more farms were visited per route, the more farms were infected. On

longer routes it was more likely that an infectious farm had more followers and consequently the virus could be transmitted to more farms. The visiting interval and the proportion of animal distribution via trade or contract selling had no significant influence, which might be explained by a possibly too small difference between the two levels. Furthermore, as visiting intervals of 14 or 21 days were assumed, it was unlikely that an infected farm sold animals more than one time during the infectious period. Consequently, it had no influence if these animals were distributed randomly by trade or directly by contract selling. On the other hand, farms that always received their animals from one farm had only this farm as an infection source, while farms with changing suppliers had multiple chances of infection via animal purchasing.

Model C

As presented by Bates et al. (2003) and Harvey et al. (2007) the control strategy had a significant impact on the course of the disease. Adding preventive culling and contact tracing resulted in a faster eradication of the epidemic at the expense of a high number of culled farms that were probably not infected. Furthermore, with every day of delay more farms were infected and preventive culling as a control measure became more effective but again at the expense of the mean number of culled farms. In this analysis it could not be distinguished between the effect of the preventive culling and the contact tracing, but it could be suggested that both had a significant influence (Kobayashi et al., 2007a,b; Kiss et al., 2005). The interaction between the delay and the control strategy indicated that control strategies with preventive culling were more effective when applied early.

5 Conclusion

The results of the sensitivity analysis with the fractional factorial design were consistent with expectations. The developed spatial and temporal Monte-Carlo simulation model was an adequate representation of real epidemics under the given assumptions. Airborne spread had an important impact on the response variables and even interactions with other factors were shown.

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Chapter 3:

Evaluation of preventive culling and emergency vaccination to eradicate foot and mouth disease epidemics

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Abstract

The effectivity of recently applied preventive culling and emergency vaccination as a possible alternative to eradicate foot and mouth disease epidemics was evaluated. Furthermore, interactions between the control strategy and the spread via air, the farm density, the type of the index case and the delay of the establishment of the control strategies were taken into account. Foot and mouth disease epidemics in a region with 729 farms were simulated with a spatial and temporal Monte-Carlo model. Different levels for the factors airborne spread (none, medium, high), farm density ($0.67, 1.05 \text{ farms}/\text{km}^2$), type of the index case (dairy, farrowing, finishing), and delay of establishment (1 day, 3 days) were defined. A basic control strategy was combined with additional preventive culling and/ or emergency vaccination within different circles. The influence of these factors was evaluated with the response variables epidemic duration, number of infected, preventively culled and vaccinated farms. The fewest farms were infected using a combined strategy of 1 km preventive culling and 10 km vaccination around each diagnosed farm in addition to the basic control strategy. Taking the number of additionally involved (preventively culled and vaccinated) farms into account, the basic strategy and vaccination around the first diagnosed farm should be preferred. A three-day delay in establishment of 1 km control strategies decreased the effectivity of emergency vaccination more than that of preventive culling. Nevertheless, emergency vaccination was effective in the eradication of FMD epidemics especially in densely populated regions.

Keywords: Foot and mouth disease, Emergency vaccination, Preventive culling, Airborne spread

1 Introduction

Foot and mouth disease (FMD) is a highly contagious *OIE list A* disease affecting all cloven-hoofed species. Control strategies to eradicate FMD epidemics in the EU are regulated by the EU Directive (2003/85/EG) (Anonymous, 2003). Movement restrictions in designated areas (protection and surveillance zone) as well as contact tracing and preventive culling can be applied after confirmation of an FMD outbreak. Since 1991 regular vaccination has been prohibited in the EU. Nevertheless, legislation provides the control measure of an emergency vaccination to eradicate FMD epidemics, particularly for regions with a high farm density or a high risk of further spread.

Both preventive culling and emergency vaccination influence the course of an FMD epidemic by reducing the susceptible population as well as virus transmission. Due to preventive culling, infected (often undiagnosed) animals are removed and from the day of application no further virus spread is possible. Emergency vaccination prevents virus spread with delay, as a stable immunity is induced some days after vaccination and virus excretion is not completely inhibited (Ferguson et al., 2001).

In recent FMD epidemics in Italy (1993), Greece (1994, 1996, 2000), the UK, Ireland, France and the Netherlands (2001) the destruction capacity limited the effectivity of preventive culling. For example, soon after the first outbreak in the Netherlands in 2001, culling and destruction capacity was insufficient to depopulate all farms (Barnett et al., 2002; Pluimers et al., 2002; Grubman, 2005). Consequently, a suppressive ring emergency vaccination was carried out to inhibit a further virus spread. Nevertheless, all vaccinated animals were culled afterwards to more quickly lift export restrictions.

The success of control strategies depends on additional factors. Delays in the establishment of control strategies reduce their effectivity (Morris et al., 2001). Rivas et al. (2003) and Traulsen et al. (2008b) suggested interactions between the control strategy and the virus spread via air, the farm density, and the index farm type.

The objective of the present study was to evaluate different control strategies using a spatial and temporal Monte-Carlo simulation model. The evaluation focused on preventive culling and emergency vaccination in different circles. Interactions between the control strategies and the virus spread via air, the farm density, the type of the index case, and the delay of establishment of the control measures were estimated.

2 Material and Methods

2.1 Description of the simulation model

A spatial and temporal Monte-Carlo simulation model was used to describe the spread of the foot and mouth disease virus (FMDV) in a given region on a daily basis. Each farm consisted of different sub-units, representing different livestock and was located by its x-/y-coordinates. The epidemic started with the infection of the index case and was able to spread via the air and via direct and indirect contacts. The course of an infection was modelled with the infection states susceptible, infected, infectious, symptoms, diagnosed and culled. Control strategies to eradicate an epidemic were implemented according to the EU Directive (2003/85/EG) (Anonymous, 2003). A detailed description of the simulation model and input parameters was given by Traulsen et al. (2008a).

2.2 Farm data

The farm data was derived from the Farm Structure Survey 2003 (Forschungsdatenzentrum, 2005). Every farm in Germany was asked about its livestock. The data set for the simulation comprised the number of animals per species on each farm in size classes and to which 'Gemeinde' (smallest administrative unit) the farm belonged. Within the administrative unit the farm was randomly distributed with the Hawth's Analysis Tool (Anonymous, 2006) for the Program ArcGIS 9.1 (ESRI, 2004).

In the present study, a region in Northern Germany with 729 farms was chosen. The farms consisted of 462 dairy cow sub-units, 412 fattening bull sub-units, 165 mother cow sub-units, 79 sheep sub-units, 49 farrowing sub-units and 59 finishing sub-units.

2.3 Emergency vaccination

Since 1991 vaccination against FMD has been prohibited in the EU. Export restrictions for animals and animal products from countries with vaccinated animal populations exist. However, in case of an FMD outbreak, particularly if a high risk of further virus transmission is present or the outbreak occurs in a region with a high animal density, legislation provides the possibility of an emergency vaccination. An emergency vaccination plan including information about the number and location of the animals to vaccinate, the vaccine, the duration and the size of the campaign has to be approved by the EU

Commission. In FMD-free countries without normal vaccination, an emergency vaccination would usually be carried out as a ring vaccination around the affected region to try to prevent outward spread, e.g. 2001 in the Netherlands (Barnett et al., 2002). In the present study, a ring vaccination around each diagnosed farm was applied.

2.4 Scenarios

Foot and mouth disease epidemics were simulated, varying the factors spread via air, the farm density, the type of the index case as well as the control strategy and its delay of establishment. For each factor different levels were defined as shown in Table 1.

Table 1: Factors and their levels for the simulation design

Factor	Levels
airborne spread	none, medium, high
farm density	0.67, 1.05 <i>farms/km²</i>
index case	dairy, farrowing, finishing farm
delay	1 day, 3 days
control strategy	B ¹ B+PC(1) ² , B+PC(2) B+Vacc(a,1) ³ , B+Vacc(a,5), B+Vacc(a,10) B+PC(1)+Vacc(a,5), B+PC(1)+Vacc(a,10) B+Vacc(f,1) ⁴ , B+Vacc(f,5), B+Vacc(f,10) B+PC(1)+Vacc(f,5), B+PC(1)+Vacc(f,10)

¹: B: Basic (protection and surveillance zone, contact tracing)

²: PC(1): preventive culling, 1: culling radius in km

³: Vacc(a,1): vaccination around each diagnosed farm, 1: vaccination radius in km

⁴: Vacc(f,1): vaccination around the first diagnosed farm, 1: vaccination radius in km

The ability of airborne virus transmission differs between virus types (Donaldson, 1979; Donaldson and Alexandersen, 2002; Kitching et al., 2006; Valarcher et al., 2007). In the present study, a distinction between none, medium and high spread via air was made. Wind from a constant direction was assumed to represent favourable conditions for airborne spread. Medium and high airborne spread differed in wind speeds (5 vs. 1.5 *m/s*) and stability classes (2 vs. 5). The two levels of farm densities (0.67 and 1.05 *farms/km²*) represented mean densities in Northern Germany. A dairy farm, a farrowing farm and a finishing farm were chosen as index cases, as these differ in their contact structure and livestock. The index case was located in the geographical centre of the region. Control

strategies were established the day after the diagnosis of a farm, or with a three-day delay, referring to the 2001 FMD epidemic in the UK (Morris et al., 2001).

Control measures according to the EU Directive (2003/85/EG) (Anonymous, 2003) were used. A basic control strategy (B) including the culling of diagnosed farms, the establishment of protection (0-3 km) and surveillance zones (>3-10 km) as well as contact tracing forwards and backwards during the previous three weeks was defined. Additionally, a preventive culling or an emergency vaccination strategy was established on all farms surrounding a diagnosed farm. To determine optimal sizes of the control measures, both were carried out in different circles: 1 or 2 km for preventive culling and 1, 5 or 10 km for emergency vaccination. Furthermore, the preventive culling strategy within 1 km was combined with the emergency vaccination within 5 or 10 km, respectively.

As described, the emergency vaccination approbation was only issued for the region that was defined in the emergency vaccination plan. The determination of this region was based on the knowledge when the first farm was detected and the FMD outbreak confirmed. Consequently, scenarios including emergency vaccination of all farms around the first detected farm were simulated. To compare vaccination around the first diagnosed farm with vaccination around each diagnosed farm the same vaccination circles (1, 5 and 10 km) were assumed.

Vaccines induced a stable immunity on average after four days and the vaccination success was determined with 98% (Ferguson et al., 2001; Visser and Thiel, 2001; Golde et al., 2005).

A full factorial design of the described factors was simulated, resulting in 504 different scenarios. As stochastic elements were included in the simulation model, each scenario was repeated 250 times.

2.5 Statistical analysis

The effectivity of the control strategies was evaluated by the mean epidemic duration in days and the mean number of infected, preventively culled and vaccinated farms. Results of Traulsen et al. (2008a) indicate that the response variables were not normally distributed. Furthermore, the most widely used model for count data is the log-linear model. For the present data, a best model fit was obtained by a negative binomial distribution and a log-link function. A ratio of the Pearson Chi-Square and the degrees of freedom (χ^2/DF) equal or close to one indicated an adequate model (Pedan, 2008). The

ratio χ^2/DF for the response variables epidemic duration, number of infected, preventively culled and vaccinated farms were 1.03, 4.34, 3.08 and 0.84, respectively. Values higher than one indicated a slight overdispersion. The GLIMMIX procedure of the SAS program package (SAS, 2006) was used to estimate the following model:

$$\begin{aligned}
\log(E(Y_{ijklm})) = & \beta_0 + air_i + density_j + index_k + control_l + delay_m \\
& +(air \times density)_{ij} + (air \times index)_{ik} + (air \times control)_{il} \\
& +(air \times delay)_{im} + (density \times index)_{jk} \\
& +(density \times control)_{jl} + (density \times delay)_{jm} \\
& +(index \times control)_{kl} + (index \times delay)_{km} \\
& +(control \times delay)_{lm}
\end{aligned}$$

where $E(Y_{ijklm})$ was the expected value of the response variable, β_0 was the overall mean, air_i was the airborne spread ($i = 1, 2, 3$), $density_j$ was the farm density ($j = 1, 2$), $index_k$ was the index case type ($k = 1, 2, 3$), $control_l$ was the control strategy ($l = 1, \dots, 13$), $delay_m$ was the delay from diagnosis until the establishment of the control strategies ($m = 1, 2$), as defined in Table 1. Moreover, $(air \times density)_{ij}$ was the two-factor interaction between the airborne spread and the farm density and so on.

The significance of the main factors and interactions was tested using Type III statistics. Least square means (LSM) were estimated on log scale. Pairwise differences between LSMs were determined with a t-test and significances adjusted using a Bonferroni-Holmes correction. The results of the models are presented by the inverse transformed values of the LS Means on log scale.

3 Results

All main factors and two-factor interactions showed a highly significant influence ($p < 0.0001$) on all response variables. The narrow 95 % confidence limits of the LSMs indicate their precise estimation (Table 2). In the following, first the influence of the main factors and second selected two-factor interactions are described.

Table 2: Inverse transformed mean (Mean), lower (CI_l) and upper(CI_u) 95 % confidence limits of the main factors airborne spread, farm density, index type and delay of establishment of control measures

		Epidemic duration			Infected farms		
		Mean	CI _l	CI _u	Mean	CI _l	CI _u
airborne spread	none	33.0 ^a	32.9	33.2	9.8 ^a	9.7	9.9
	medium	102.0 ^b	101.6	102.4	222.3 ^b	220.2	224.4
	high	104.3 ^c	103.9	104.7	387.1 ^c	383.5	390.8
farm density (<i>farms/km</i> ²)	0.67	69.6 ^a	69.4	69.8	79.6 ^a	78.9	80.2
	1.05	71.5 ^b	71.3	71.7	112.1 ^b	111.2	113.0
index type	dairy	78.9 ^a	78.6	79.2	144.1 ^a	142.8	145.5
	farrowing	66.6 ^b	66.4	66.9	75.7 ^b	75.0	76.5
	finishing	66.9 ^b	66.6	67.1	77.2 ^c	76.5	78.0
delay	1 day	65.4 ^a	65.2	65.6	74.2 ^a	73.6	74.8
	3 days	76.1 ^b	75.9	76.5	120.2 ^b	119.3	121.3

^{a,b,c}: different letters indicate significant differences within response variable and factor, $\alpha=0.05$

Main factors

The greatest differences between the factor levels were observed considering airborne spread (Table 2). If the FMDV was not transmitted by air, epidemics lasted on average 33 days and 9.8 farms were infected. With airborne spread, epidemics were significantly longer and more farms were infected. While the epidemic duration was constant between the levels medium and high airborne spread, the number of infected farms increased significantly for high airborne spread.

Differences between the levels of the factors farm density, index type and delay of establishment of the control zones were less than for airborne spread (Table 2). Long-lasting FMD epidemics with a high number of infected farms were estimated for densely populated regions if the index case was a dairy farm or if control measures were established with a three-day delay.

Epidemics eradicated with the basic control strategy lasted 84 days and 123 farms were infected (Table 3). Additional control measures within the 1 km zone (B+PC(1), B+Vacc(a,1), B+Vacc(f,1)) decreased the number of infected farms. Within these control strategies, no significant differences in the number of infected farms were observed, but the number of additionally involved farms by each control strategy (preventively culled or vaccinated) were significantly different. The preventive culling strategy resulted in 72 preventively

culled farms, while vaccination only affected 15 respectively 1 farm.

Table 3: Inverse transformed mean epidemic duration (dur) in days, mean number of infected (inf), preventively culled (prev) and vaccinated (vacc) farms depending on the control strategy

	dur	inf	prev	vacc
B ¹	84.3 ^a	124.5 ^a	-	-
B+PC(1) ²	76.0 ^b	122.8 ^b	72.3 ^a	-
B+PC(2)	70.9 ^c	108.0 ^c	132.4 ^b	-
B+Vacc(a,1) ³	78.1 ^a	119.1 ^b	-	15.0 ^a
B+Vacc(a,5)	64.1 ^d	87.6 ^d	-	196.9 ^b
B+PC(1)+Vacc(a,5)	62.8 ^d	80.7 ^e	53.7 ^c	171.2 ^c
B+Vacc(a,10)	51.1 ^e	62.7 ^f	-	392.0 ^d
B+PC(1)+Vacc(a,10)	50.0 ^e	57.9 ^g	30.4 ^d	348.9 ^e
B+Vacc(f,1) ⁴	83.5 ^{af}	120.0 ^b	-	0.7 ^f
B+Vacc(f,5)	84.3 ^f	110.2 ^{bc}	-	40.9 ^g
B+PC(1)+Vacc(f,5)	75.0 ^b	97.1 ^h	71.9 ^a	45.3 ^h
B+Vacc(f,10)	73.5 ^g	82.5 ^e	-	170.0 ^c
B+PC(1)+Vacc(f,10)	66.3 ^h	73.4 ⁱ	53.0 ^c	192.6 ^b

^{a,...,i}: different letters indicate significant differences within response variable and factor, $\alpha=0.05$

¹: B: Basic (protection and surveillance zone, contact tracing)

²: PC(1): preventive culling, 1: culling radius in km

³: Vacc(a,1): vaccination around each diagnosed farm, 1: vaccination radius in km

⁴: Vacc(f,1): vaccination around the first diagnosed farm, 1: vaccination radius in km

Increasing the size of the eradication circle decreased the number of infected farms. Preventive culling within 2 km (B+PC(2)) and vaccination within 5 km around the first diagnosed farm (B+Vacc(f,5)) resulted in comparable numbers of infected farms, 108.2 and 110.2 respectively. The combination of this vaccination strategy with 1 km preventive culling (B+PC(1)+Vacc(f,5)) decreased the number of infected farms significantly, compared to both control measures alone. Applying the 5 km vaccination around each diagnosed farm (B+Vacc(a,5)) resulted in fewer infected farms than vaccination around the first diagnosed farm, both for the vaccination alone and for the combination with 1 km preventive culling. Taking the number of additionally involved farms into account showed that although fewer farms were infected with vaccination around all diagnosed farms, many more farms were involved in total compared to vaccination around the first diagnosed farm. Applying vaccination in a 5 km circle around each diagnosed farm meant that

almost twice as many farms were involved as with vaccination around the first diagnosed farm.

10 km vaccination circles additionally reduced the number of infected farms. The fewest farms were infected with the combined strategy of 1 km preventive culling and 10 km vaccination around each diagnosed farm (B+PC(1)+Vacc(a,10)). Regarding the number of totally involved farms, again twice as many farms were affected with vaccination around each diagnosed compared to the first diagnosed farm.

In general, the fewest farms were affected with the basic control strategy. Reductions in the number of infected farms was possible with additional preventive culling as well as emergency vaccination. The larger the eradication circle, the fewer farms were infected, but the more farms were involved.

Two-factor interactions

As described, a dairy farm as the index case results in a severe course of the FMD epidemic. But the significant interaction between the type of the index case and the virus spread via air (Figure 1) indicated that with spread via air the farrowing farm as the index case resulted in a higher epidemic size. In contrast, without airborne spread more farms were infected if the epidemic started on a dairy farm.

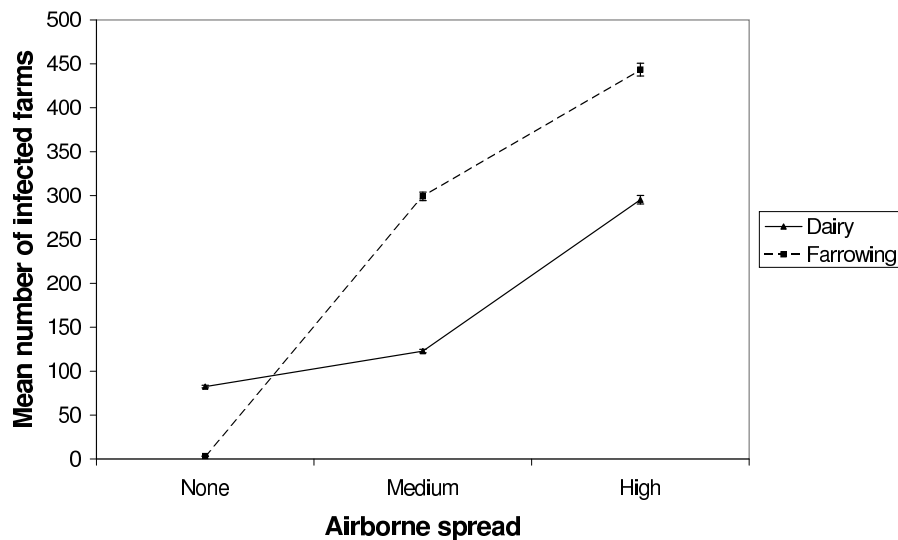


Figure 1: Two-factor interaction between airborne spread and index type

Taking the delay of establishment into account, the differences between the control strategies infecting the most and the fewest farms reduced when established with a three-day delay (Figure 2). Comparing the control strategies applied within a 1 km circle a three-day delay increased the differences between the control strategies and preventive culling

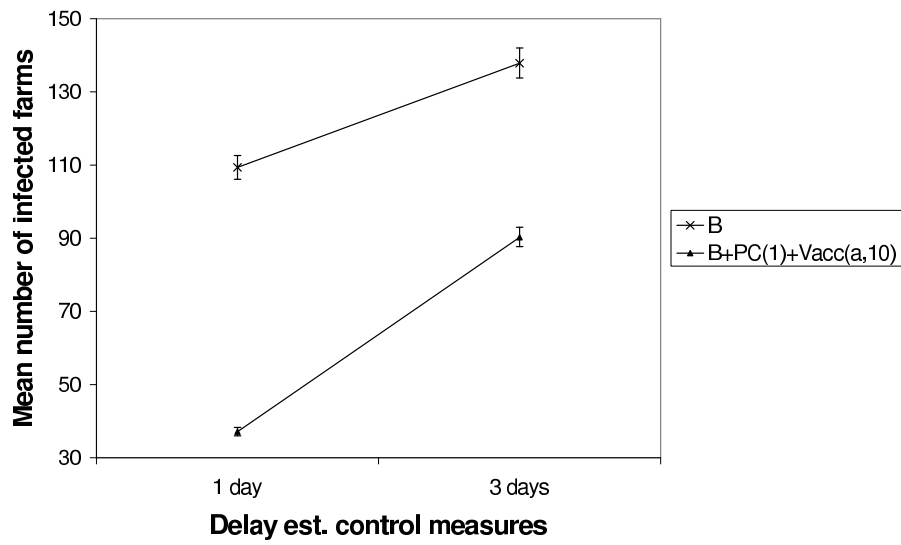


Figure 2: Two-factor interaction between the delay of the establishment of the control strategies and selected control strategies

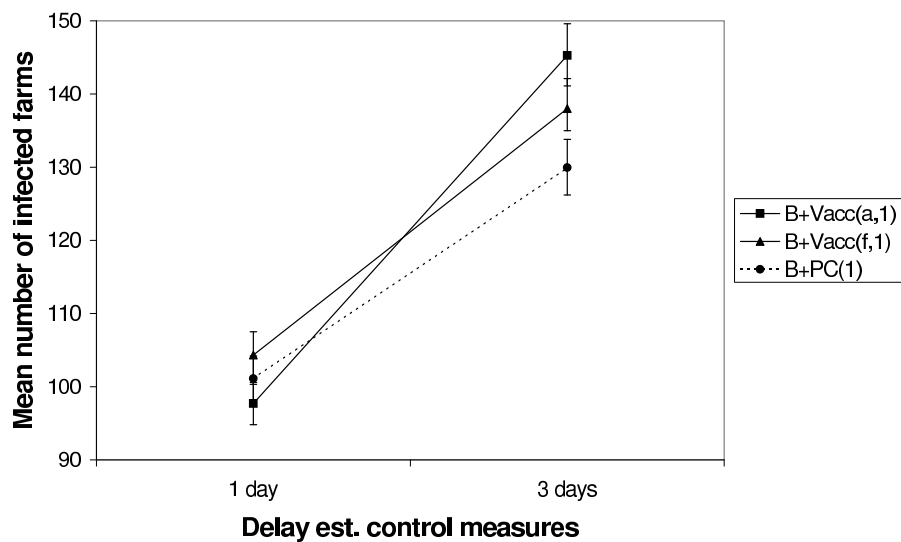


Figure 3: Two-factor interaction between the delay of the establishment of the control strategies and selected control strategies

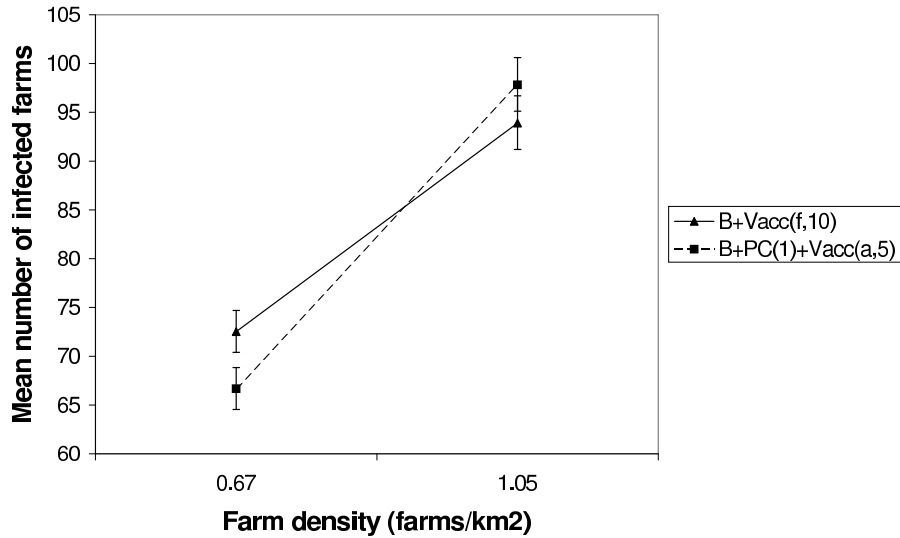


Figure 4: Two-factor interaction between the farm density ($farms/m^2$) and selected control strategies

was favourable (Figure 3).

Figure 4 shows that in sparsely populated regions the combined strategy of 1 km preventive culling and 5 km vaccination around each diagnosed farm resulted in fewer infected farms than 10 km vaccination around the first diagnosed farm.

4 Discussion

In general, the fewest farms were infected with the combined strategy of 1 km preventive culling and 10 km vaccination around each diagnosed farm. Cost-benefit analysis of foot and mouth disease control strategies in the UK estimated as well a 10 km vaccination as an effective strategy, compared to culling of infected and dangerous contacts herds. Particularly in large epidemics, 15 to 50% fewer premises were infected (Anonymous, 2005). However, within a 10 km eradication circle a large number of farms had to be culled preventively or vaccinated, respectively. Taking these numbers into account, the choice of the control strategy had to be adopted to differences in airborne spread, the farm density in the region, the species on the index case and the expected delay of establishment of the control strategy.

Results of the present analysis confirmed studies by Bates et al. (2003) and Kobayashi et al. (2007) that in general in epidemics starting on a dairy farm more farms are infected than starting on a pig farm. More contacts concerning the distribution of the animals and regular contact of the bulk milk tanker could be the cause of the difference. Present results

show that taking airborne spread into account, a pig farm as the index case induces more severe epidemics. Pigs excrete more virus via the air than ruminants (Sørensen et al., 2000; Alexandersen et al., 2003) and in the present study favourable weather conditions for airborne spread were assumed. The FMDV can be spread easily and widely via air and even interfered with the transmission via animal contacts and via the bulk milk tanker. In the present study, no control strategy was preferential regarding different index types. Nevertheless, in reality differences between the effectivity of control measures can be suggested. In the simulation model, no restrictions concerning the feasibility of control measures were assumed, e.g. personnel resources, equipment, vaccine availability or destruction capacity. But if resources are limited, results indicate that the ability of airborne spread of the present virus type has to be taken into account. If no airborne spread is likely, dairy farms should be preferred when establishing control strategies, with airborne spread pig farms.

Taking the farm density into account, the present results showed that the severe epidemics in densely populated regions were best eradicated using large vaccination circles. Nevertheless, it was sufficient to vaccinate around the first diagnosed farm, compared to vaccination around each diagnosed farm. In regions with a low farm density epidemics were smaller. Consequently, interactions showed that smaller eradication circles were sufficient if vaccination was applied around each diagnosed farm and it was also preventively culled. Although this strategy resulted in fewer infected farms, the increasing number of additionally involved farms required more resources for its implementation.

A three-day delay in the establishment of the control strategies reduced their effectivity as more farms were infected. These results confirm studies by Morris et al. (2001), who analysed data from the 2001 FMD epidemic in the UK. They estimated that delays in the culling of animals on infected farms beyond 24 hours after diagnosis slightly increased the epidemic size. Furthermore, failure to achieve preventive culling on an adequate number of at-risk farms substantially increased the expected size of the epidemic. The interactions of the present study indicate that the effectivity of emergency vaccination strategies decreased more than preventive culling strategies if established with delay. Although both strategies were established at the same time, preventive culling inhibits virus transmission immediately, while a stable immunity in vaccinated animals is established after a few days (Ferguson et al., 2001). However, this time-until-immunity delay of the vaccination reduced the effectivity only if the vaccination had already started with a three-day delay.

If vaccination was applied immediately, no negative effects were observed. Consequently, for vaccination strategies, a rapid establishment is more important than for preventive culling strategies. If resources needed for the establishment of the control strategies are limited or the immediate establishment cannot be guaranteed, preventive culling would be more effective than emergency vaccination. Due to current legislation, a delay in the establishment of an emergency vaccination is more likely than for preventive culling. The approbation of the emergency vaccination plan by the EU lasts a few days. According to the present results, a rapid approval process could increase the effectivity on an emergency vaccination campaign. However, the definition of the region to be vaccinated already when the approbation for emergency vaccination is issued no negative effects. Vaccination in a larger vaccination circle around the first diagnosed farm was at least as effective as vaccination in smaller circles around each diagnosed farm. Additionally, fewer farms were additionally involved.

Preventive culling as well as the emergency vaccination of farms require high logistical, personnel and material effort (Berkenhoff et al., 2003). In addition to the number of infected, preventively culled and vaccinated farms, the availability and costs of these resources and economic consequences have to be taken into account. Prolonged export restrictions are valid after the application of emergency vaccination compared to after preventive culling measures. Evaluating emergency vaccination, the availability of sufficient doses of vaccines and the development of carrier animals have to be taken into account (Ganter et al., 2001; Alexandersen et al., 2002; Müller et al., 2001; Grubman and Baxt, 2004). With regard to the preventive culling strategy sufficient destruction capacity has to be allocated.

5 Conclusion

In conclusion, no general optimal control strategy could be defined. It became clear that besides the type of the index case also the ability of airborne transmission of the virus has to be taken into account. A rapidly established emergency vaccination strategy in a large circle around the first diagnosed farm was more effective than preventive culling around all infected farms in a small circle. Combined strategies of preventive culling and emergency vaccination were beneficial in sparsely populated regions. In contrast, in regions with a high farm density larger eradication circles with an emergency vaccination were favourable.

Evaluating the control strategies not only with the number of infected farms, but with the additionally involved farms, the basic strategy or additionally vaccination around the first diagnosed farm should be preferred.

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Chapter 4:

A Fuzzy-Logic inference system of the transmission of foot and mouth disease virus by air

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Abstract

The aim of the present study was to evaluate whether Fuzzy-Logic can adequately estimate the concentration of foot and mouth disease at a certain farm located downwind after release from another farm. The Gaussian Dispersion model was used as a reference model. Weather recordings from the airport in Vienna, Austria, in 2004 were available as input parameters. A Fuzzy-Logic inference system (FIS) was generated using neuro-adaptive learning techniques with one part of the data set. The rest of the data was used for validation. In a ten-fold cross-validation design the generalisation of the FIS was evaluated. The goodness-of-fit of the FIS to the Gaussian Dispersion model was tested using a regression from the difference in the output on the sum of the output. An F-Test was used to test the equality to zero of the regression coefficients.

The mean virus concentration was the same for both models. The variance in the virus concentration of the FIS was much smaller than that of the Gaussian Dispersion model. Low concentrations were underestimated while high concentrations were overestimated. The results indicated that Fuzzy-Logic can be used to estimate airborne spread of FMDV. Further research is necessary for determine a better adjustment of the membership functions.

Keywords: Foot and mouth disease, Airborne spread, Fuzzy-Logic, Gaussian Dispersion model

1 Introduction

Foot and mouth disease virus (FMDV) can spread rapidly and widely by air among all cloven-hoofed animals (Donaldson et al., 2001; Kitching et al., 2005). Airborne spread is determined on the one hand by the number and species of the animals on the source farm as well as the virus type and the species and number of animals located downwind (Donaldson, 1979; Gloster and Alexandersen, 2004; Mahy, 2005; Gloster et al., 1981). On the other hand, the weather parameters temperature, relative humidity, wind speed, wind direction and precipitation influence the ability of airborne spread (Gloster et al., 1981, 1982)

Airborne spread has often been estimated using the Gaussian Dispersion model (Gloster et al., 1982, 2003; Sørensen et al., 2000, 2001). It provides a good approximation for airborne virus spread, but neglects certain influence factors such as topography, changing wind directions and relative humidity. Lagrangian Particle models incorporate topography and time-variant meteorological conditions and provide a better estimation of the airborne spread of FMDV (Mayer et al., 2007). Unfortunately, the Lagrangian Particle model is really complicated and needs a variety of weather input parameters, which are complex to measure.

Statements such as: advantageous weather conditions for airborne spread were a relative humidity of minimum 65-70%, medium temperatures, medium and lower wind speeds from a constant direction and stable atmospheric conditions can often be found (Donaldson, 1979; Gloster et al., 1982, 2003, 2004, 2005). But concrete values for a 'medium' temperature or other parameters can hardly be found.

Fuzzy-Logic provides the opportunity to transfer these linguistic variables into membership functions (Zadeh, 1965). A realistic range of the temperature is defined. Temperature is modelled with the membership functions, e.g. 'low', 'medium' and 'high'. Each temperature on the realistic scale belongs with a certain membership (e.g. 0.2 or 0.8) to one or more of the defined functions. The exact definition of a 'medium' temperature is unnecessary. Consequently, the idea arises to create a simple Fuzzy-Logic inference system based on datasets of weather parameters that could be collected as easily as possible in order to estimate the FMDV transmission.

In the present study, a Fuzzy-Logic inference system for FMDV transmission by air was to be developed. It was compared to the Gaussian Dispersion model to evaluate whether

Fuzzy-Logic could be an appropriate technique to model FMDV transmission via air.

2 Material and Methods

The Fuzzy-Logic inference system (FIS) was created using the ANFIS function of the Fuzzy-Logic Toolbox of MATLAB (MathWorks, 2005). Input and output data of the Gaussian Dispersion model were used to estimate a Sugeno FIS (Sugeno, 1985). The output of the FIS was validated by cross-validation. The goodness-of-fit was tested by a regression analysis described by Kleijnen et al. (1998).

2.1 Parameter and data

The input and output parameters of the Gaussian Dispersion model were used for the Fuzzy-Logic model, to allow a direct comparison of the two models. The wind speed (m/s), the stability class, the virus emission rate ($TCID_{50}/s$), and the x and y coordinates (m) of the recipient farm were the input and the virus concentration at the recipient farm ($TCID_{50}/m^3 \cdot day$) the output parameter ($TCID_{50}$: 50% tissue culture infectious dose).

The available weather data for the present study were recorded at the airport in Vienna, Austria, during the year 2004 (Mayer, 2007). The sampling interval was half an hour, so that in total 17,559 data sets were available. Average weather conditions of each week were calculated and resulted in 19 different combinations of the wind speed and stability class. Six classes of virus emission rates were assumed. They represented the range of emission rates of farms with 10 to 1000 cattle, sheep and pigs, respectively. As the Gaussian Dispersion model is applicable within a 10 km circle, the x and y co-ordinates were varied between 0.01 and 10 km. Analysis of the output of the Gaussian Dispersion model with the present weather data showed that large differences occurred within the 1 km distance. Consequently, the classes for x and y varied up to 1 km in 100 m steps and above in 500 and 1000 m, respectively. In total a data set of 58,720 combinations of the input parameters were used to develop the FIS. Statistical parameters of the input parameters are shown in Table 1.

Table 1: Mean, standard deviation (std), minimum (min) and maximum (max) of the input parameters, n=54,720

	unit	mean	std	min	max
windspeed	m/s	4.89	3.06	1.00	12.00
stability class		4.21	0.61	3.00	5.00
emission rate	$TCID_{50}/s$	$7.80 \cdot 10^5$	$1.72 \cdot 10^6$	0.30	$4.63 \cdot 10^6$
x	m	$4.04 \cdot 10^3$	$3.45 \cdot 10^3$	100.00	$10.00 \cdot 10^3$
y	m	$2.98 \cdot 10^3$	$3.25 \cdot 10^3$	10.00	$10.00 \cdot 10^3$

2.2 The Gaussian Dispersion model

The Gaussian Dispersion model calculates the concentration of FMDV for each point within a 10 km circle around the source farm with the following model:

$$\bar{c}(x, y, z) = \frac{Q}{2\pi\bar{u}\sigma_y\sigma_z} \exp\left(-\frac{y^2}{2\sigma_y^2}\right) \left[\exp\left(-\frac{(z-h)^2}{2\sigma_z^2}\right) + \exp\left(-\frac{(z+h)^2}{2\sigma_z^2}\right) \right]$$

$$\sigma_y = B\left(\frac{x}{u}\right)^\beta, \sigma_z = A\left(\frac{x}{u}\right)^\alpha$$

The concentration \bar{c} is measured in $TCID_{50}/m^3 \cdot day$. It is calculated depending on the wind speed \bar{u} in m/s , the virus emission rate Q in $TCID_{50}/s$, the coordinates of the destination farm x, y, z and the virus emission high h in m . The source farm is located at the coordinates (0,0). The dispersion parameters σ_y and σ_z depend on the atmospheric stability parameters B, β, A and α defined in the ÖNORM 1992 (Anonymous, 1992).

2.3 The Fuzzy-Logic inference system

The large size of the available data set and the presence of both input and output data allowed the application of neuro-adaptive learning techniques to generate the FIS (Sugeno, 1985; Jang and Sun, 1997). Using subtractive clustering (Chiu, 1994) the number of clusters and the clusters centres were estimated. Based on these clusters, the membership functions of the FIS were generated. The generalisation of the FIS was evaluated with a ten-fold cross-validation (Haykin, 1999). The available data set was randomly divided into ten subsets of equal size (5,782 observations each). The FIS was trained on all the subsets except for one. The training procedure used a combination of the backpropagation algorithm and a least square method and performed 200 Epochs, which were a common

choice (MathWorks, 2005). The validation error was determined by testing the generated FIS on the subset left out. This procedure was repeated for ten trials, each time using a different subset for validation. The performance of the FIS was assessed by averaging the error under validation over all the trails.

2.4 Kleijnen Test

The data sets for the validation were applied to both the Gaussian Dispersion model and to the FIS. This allowed a direct comparison of the corresponding output values (virus concentration).

Usually the goodness-of-fit of a model is assessed using scatter-plots of the estimated and true values. Additionally, it can be tested whether a linear regression with the coefficients $\beta_1 = 1$ and $\beta_0 = 0$ can be fitted. Kleijnen et al. (1998) described that this method tended to reject a valid simulation model. They described an alternative regression method using the differences and the sums of the actual and desired output. Fitting a linear regression from the sum on the difference to these data with the coefficients $\gamma_1 = 0$ and $\gamma_0 = 0$ is a better measure for the goodness-of-fit of models. An F-Test was to be used to determine whether the regression coefficients were equal to zero. In the present study, the REG procedure (SAS, 2003) was used for regression analysis.

3 Results

For each of the ten validation data sets the mean and the variance in the output parameter (virus concentration) were calculated. Averages over the ten data sets are presented in Table 2.

Table 2: Mean, minimum, maximum and variance of the virus concentrations over all the 10 subsets, depending on the estimation model

	Gauss	FIS
mean	1.97	1.95
variance	2,326.32	103.83
minimum	0	-55.25
maximum	3554.8	161.53

The results show that the mean virus concentration estimated with the FIS was almost identical to that of the Gaussian Dispersion model (1.95 compared to 1.97). In contrast,

the variance was different. The variance in the output of the FIS, 103.83, was much smaller than that of the Gaussian Dispersion model, 2326.32. Conform to the low variance of the FIS' virus concentration, the maximum concentration was much lower than for the Gaussian Dispersion model. The Kleijnen Test showed for none of the ten trials a satisfactory fit between the output of the Gaussian Dispersion model and the FIS (results not shown).

The goodness-of-fit was determined for different ranges of the virus concentration. Each of the ten subsets was classified with the virus concentrations estimated with the Gaussian Dispersion model. It was distinguished between low ($< 5 TCID_{50}/m^3 \cdot day$), medium (5-50 $TCID_{50}/m^3 \cdot day$) and high ($> 50 TCID_{50}/m^3 \cdot day$) virus concentrations (Table 3).

Table 3: Mean and variance in the virus concentrations over all the ten subsets, depending on the estimation model and the virus concentration estimated with the Gaussian Dispersion model

c_{Gauss}	$mean_{Gauss}$	$mean_{FIS}$	var_{Gauss}	var_{FIS}
low	0.12	1.6	0.48	86.84
medium	21.28	29.08	113.37	411.59
high	415.28	42.77	395,679.11	526.77

Comparison of the average virus concentration and its variances indicated that the generated FIS overestimated low virus concentrations, while high concentrations were underestimated. Nevertheless, the virus concentrations of the medium class were estimated sufficiently with the FIS.

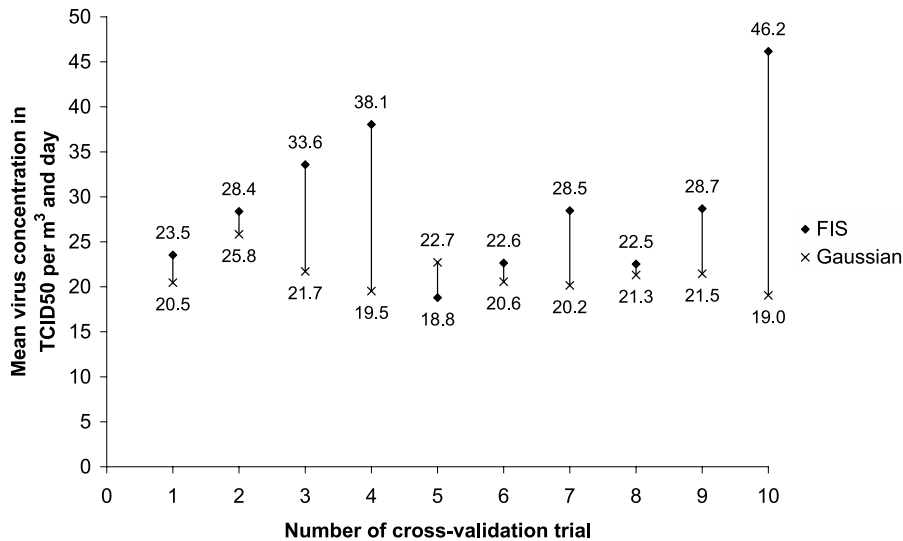


Figure 1: Mean virus concentrations of the Gaussian Dispersion model and the FIS depending on the ten trials for medium virus concentrations

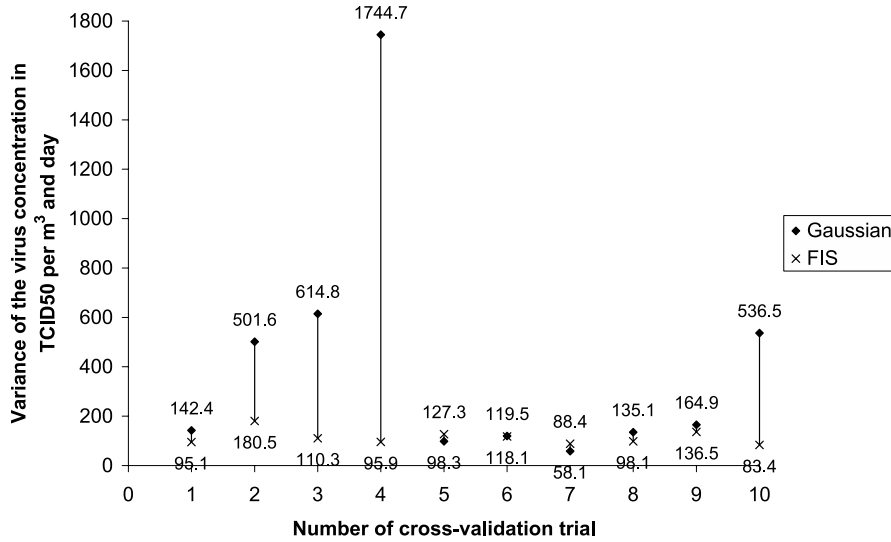


Figure 2: Variances in the virus concentrations of the Gaussian Dispersion model and the FIS depending on the ten trials for medium virus concentrations

The Figures 1 and 2 show the detailed results of the ten trials of the medium class. The mean virus concentration of the Gaussian Dispersion model and the FIS differed between the ten trials from minimum 1.2 to maximum 27.1. The same was observed for the variance in the virus concentration. A minimum difference of 1.4 and maximum of 1648.8 was obtained. Nevertheless, for the folds one, five, six, eight and nine the average virus concentration as well as the variance showed only small differences. Performance of the Kleijnen Test indicated an adequate model fit (Table 4). The F-Test confirmed that the estimated regression coefficients were not different from zero. Consequently, medium virus concentrations were estimated adequately using Fuzzy-Logic.

Table 4: Regression coefficients and significances of the F-Test for the Kleijnen Test of medium virus concentrations

Fold	γ_0	p	γ_1	p
1	3.51	0.5246	-0.15	0.2032
2	23.85	0.0255	-0.49	0.0075
3	23.23	0.0006	-0.63	<.0001
4	29.86	<.0001	-0.84	<.0001
5	0.20	0.9718	0.09	0.4762
6	-1.87	0.7590	-0.00	0.9713
7	-16.39	0.0347	0.17	0.2656
8	5.23	0.5768	-0.15	0.4681
9	-3.72	0.5469	-0.07	0.5422
10	15.19	0.0558	-0.65	<.0001

4 Discussion

The generated FIS was an adequate model to estimate the mean virus concentration, although low and high concentrations were overestimated and underestimated, respectively. A reason for the under- and overestimation might be that most of the virus concentrations of the data set to generate the FIS were zero. For an airborne spread of FMDV up to 10 km, favourable weather conditions (low virus dispersion, high virus survival) as well as a high amount of virus excretion (pigs in acute stages) are required (Donaldson, 1979; Gloster et al., 2003, 2005). High virus concentrations were less frequent. As the model was generated using neuro-learning techniques, the small frequency of the high virus concentration might have lead to their underestimation. Furthermore, no restrictions for the range of the concentration were defined in the present study. In further analysis a minimum of zero should be assumed. An alternative to the automatic generation of the membership functions in the Sugeno model are Mamdani techniques (Mamdani and Assilian, 1975). The membership functions are constructed based both on the available data set and on expert knowledge. Furthermore, even the output variable is defined with membership functions. Modelling of an extract of the possible combination of the input variables with a Mamdani FIS (results not shown) indicated that higher variances could be achieved.

The validation of the FIS was carried out by adjusting the FIS' output to the output of the Gaussian Dispersion model. Although the Gaussian Dispersion model is a widespread and established method in epidemiology, it neglects some parameters that have an influence on airborne spread. The present study indicated that Fuzzy-Logic could be used to model the same as the Gaussian Dispersion model. Further developments of the FIS should include additional parameters to allow a more detailed modelling. As described, the Lagrangian model included more parameters but at the expense of a quite complex model. In contrast to the Lagrangian model, the FIS should stay simple and include only parameters that are easy to collect. The output of an extended FIS should determine whether a farm at a certain location would be infected. The model should determine first, how much virus is excreted, second, how much arrives at a certain point and third, whether it is sufficient to infect the farm.

5 Conclusion

The aim of the present study was to evaluate whether Fuzzy-Logic is an adequate technique to estimate the spread of FMDV via air. Comparisons to the Gaussian Dispersion model indicated that the average virus concentration could be estimated accurately. However, the variance in the FIS' estimations was too small. Low virus concentrations tended to be overestimated, while high were underestimated. Nevertheless, the estimation of the medium virus concentrations was adequate. Consequently, the present results showed that Fuzzy-Logic can be used to model the spread of FMDV via air, but models have to be adjusted to obtain a larger variance in the output. Further research should take the application of a Mamdani FIS into account.

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General Discussion

The aim of the present study was to develop a simulation model for the epidemiology and control of the foot and mouth disease virus (FMDV). Special emphasis was given to the modelling of airborne spread. Different control strategies were evaluated considering interactions with factors such as airborne spread, the regional farm density, the type of the index case and the delay of the establishment of the control strategies. Finally, a Fuzzy-Logic inference system for airborne spread was developed and compared to the Gaussian Dispersion model.

The simulation model

The simulation model presented in Chapter One is based on the Monte-Carlo technique. Monte-Carlo models represent the stochastic process of an epidemic by drawing random numbers from designated distributions.

Classical epidemiological models (SIR models) are based on the Markov technique. The Markov chain describes a stochastic process during which the defined individuals (farm, animal) move from one state to another. The general SIR model includes the three states susceptible 'S', infected 'I' and recovered 'R', but can be extended with additional states (Durand and Mahul, 2000; Ferguson et al., 2001). In contrast to Monte-Carlo methods, inhomogeneity in the contact process, due to the spatial distribution of the individuals and differences in the farm density and the population size, cannot be taken into account in a simple SIR model (Jørgensen et al., 2000; Höhle and Jørgensen, 2002).

Monte-Carlo models can consider the uncertainty of input parameters and even unknown parameters of which the true value is difficult or impossible to obtain (Thrusfield, 1995). Input parameters describing the virus transmission can be derived from recent epidemics as well as laboratory analysis. Parameters estimated in laboratory analysis are often determined using small sample sizes so that the exact transferability of these values to real epidemics is doubtful (Sørensen et al., 2000; French et al., 2002). Estimation of

parameters from recent epidemics can be biased. For example, exact determination of the infection date of a farm can be estimated considering the age of the clinical lesions at the time of diagnosis (Gloster et al., 2003). Nevertheless, biological boundaries can be determined. Consequently, important parameters that are uncertain or cannot even be measured can be included in a simulation model using Monte-Carlo methods.

In the present simulation, the farm, consisting of sub-units, was regarded as the modelling unit. In contrast to previous models this allowed an arbitrary composition of different livestock for each farm. This structure provided the opportunity to include elements of agent-based simulation methods. Hitherto, events occurring in a sub-unit only depended on the type of livestock and for airborne spread also on the number of animals. According to the agent-based method other determinants, modelling the decision character of the farm manager, could be taken into consideration. The farm became more individual and the model more realistic.

Within-farm spread was neglected in the present simulation. Starting with the day of infection all animals within the whole farm were regarded as infected. The division into sub-units could be used to estimate virus transmission within the farm, e.g. the disease started in the farrowing sub-unit of a farm and when an according finishing sub-unit would be infected was then estimated. A further extension would be to model the whole infection process on an animal basis. Combined models including both within- and between-farm spread have to fulfil different constraints. Within a farm the spread has to be estimated distance-independently. It depends on the type and number of the livestock. Between-farm spread has to take distances into account and with regard to contacts, animals of one farm have to be considered as a whole. Special models have been developed to estimate within-farm spread (Carpenter et al., 2004), e.g. a deterministic Reed-Frost model used by Bates et al. (2003a,b). An alternative method might be the use of cellular automata. The modelling unit is a cell that can switch between defined states. Each cell interacts with other cells within the local neighbourhood. These interactions are controlled by a set of rules concerning the neighbourhood and cell states at earlier time stages (Doran and Laffan, 2005). Transferring to an animal disease, each animal could be represented as a cell. Animals that are kept in one stable are modelled as cells in proximity. Although this model can take spatial and temporal aspects into account, the cells are normally unable to directly communicate on a global scale, e.g. animal distribution, bulk milk tanker. Consequently, virus transmission between farms is hard to estimate. Doran and Laffan

(2005) used a cellular automata model to estimate FMDV spread among feral pigs in Australia. The cell was defined by the feral pig density in a certain area. This approach might be used to estimate FMDV spread from animal to animal among grazing animals, such as cattle and sheep.

The routing problem

Possibilities of virus transmission are differentiated into direct animal-to-animal contacts and indirect contacts with the veterinarian, animal feed vehicle and bulk milk tanker as well as airborne spread. In the present model the pattern of the contacts is modelled by a routing problem. Existing models, e.g. of Bates et al. (2003a) and Kobayashi et al. (2007), computed virus transmission of contacts using the probability of a farm of having a contact on the actual day and a contact-specific transmission probability. This modelling scheme assumes that the infection probabilities of the farms are independent. But while modelling the virus transmission of vehicles or personnel moving from one farm to another, virus transmission occurs only in the order of a route and is not independent. Direct followers of an infected farm have a higher probability of being infected than subsequent followers. Furthermore, the exposure to doses below the minimum amount of virus will not result in disease, whereas doses above this will result in infection with increasing probability (Donaldson, 1997; Sørensen et al., 2000). French et al. (2002) developed dose-response curves for cattle and sheep. They concluded that the beta-poisson model was not an appropriate model of the relationship of dose and response. Furthermore, a single virus particle has a non-zero probability of initiating infection. In the present model, an exponential function was used to model both the decrease in transmission probability with the increasing number in the order and the increase of infection probability with the dose.

The routes were computed based on the Euclidean distance between farms and consequently neglecting the road structure. Rivas et al. (2003) found a significant impact of the road density on the course of an epidemic, especially in the early stages of an epidemic. Savill et al. (2006) concluded in an analysis of the 2001 FMD epidemic in the UK that a simple spatial kernel based on the Euclidean distance was sufficient for most regions. Moreover, in the present study the reduction of the transmission probability depends only on the number of the follower and not the distance. It might be suggested that the inclusion of the road structure also needs the inclusion of the length of the 'driven'

distance between farms. However, as contradictory results were found and to keep the model simple, this aspect was neglected.

Validation of the simulation model

The aim of a validation is to test whether a simulation model is an acceptable representation of the corresponding real system, given the purpose of the simulation model (Law and Kelton, 1982). A fractional factorial design of a sensitivity analysis was performed to validate the developed simulation model. If only output data and expert knowledge exist, sensitivity analysis is recommended, e.g. by Kleijnen (1999). Trace-driven analysis including regression analysis or bootstrapping (Kleijnen, 1999) cannot be performed, as real data are rare.

In a sensitivity analysis, the reaction of the simulation output to extreme values of the models input can be investigated. Moreover, it shows which factors are important and whether a factor has effects that conform to the experts knowledge. Karsten et al. (2005), Bates et al. (2003b) and Menach et al. (2005) used a sensitivity analysis to validate their models for the spread of classical swine fever and foot and mouth disease spread, respectively.

The developed simulation model uses a high number of input factors, considering the virus transmission, but also the characteristics of the control strategies. In the present study, validation factors were chosen with regard to the purpose of the simulation model (Law and Kelton, 1982; Sargent, 2003). The purpose was the evaluation of control strategies, considering interactions with certain influencing factors. The success of control strategies depends on additional factors: the virus spread via air, the farm density, the index farm type and delays in the establishment of control strategies (Morris et al., 2001; Rivas et al., 2003). Furthermore, factors describing the characteristics of the virus type, such as the incubation period, the time from infection until detection and the time from the onset of clinical symptoms until diagnosis were considered to check the correct modelling of the virus spread.

Different levels of each parameter were defined and represented the realistic range of the parameters for the different virus types. Assuming only two levels for each parameter, the number of scenarios to simulate a full design grows exponentially. A very efficient screening design when only main factors are of interest was introduced by Plackett and Burman (1946). Eleven factors can be estimated with only twelve scenarios. Interactions

between the main effects are used to estimate other main effects. Nevertheless, for the present study interactions between the factors were suggested (Morris et al., 2001; Rivas et al., 2003). A 2^{k-p} fractional factorial design is applied to estimate main factors as well as two-factor interactions (Box and Hunter, 1961a,b). In such a design, only higher-order interactions between main factors are used to estimate other main factors. More scenarios have to be performed compared to the Plackett and Burman design, but nevertheless fewer than in a full design.

Control strategies for FMD

The establishment of preventive culling zones in previous FMD epidemics results in a high number of depopulated farms, although the majority of the culled farms is not infected. The results of Chapter Three indicate that emergency vaccination is an effective alternative to preventive culling. In the present study, the control strategies were evaluated regarding the epidemic duration and number of infected, preventively culled and vaccinated farms. Additionally, both preventive culling and emergency vaccination of farms require a high logistical, personnel and material effort (Berkenhoff et al., 2003). Their availability and costs as well as economical consequences have to be taken into account. Evaluating emergency vaccination, the availability of sufficient doses of vaccines has to be considered. Antigen banks store a certain stockpile of doses of the contemporary strains circulating in the regions from which the greatest risk of introduction is perceived (Alexandersen et al., 2003). An immunity, induced with a vaccine or an infection against one strain, provides almost no immunity against another strain of the same type (Alexandersen et al., 2003; Kitching et al., 2005). Consequently, in case of an outbreak a rapid identification of the present virus type is required to have the accordant vaccine available for an emergency vaccination. One million ready-to-use vaccine doses have to be available four days after application of the EU and an additional four million ten days after application (Anonymous, 2003). Due to these restrictions the assumed three-day delay until establishment of the emergency vaccination was an optimistic assumption.

Current legislation states that countries with FMDV present are subject to export restrictions (Anonymous, 2003). If an FMD epidemic is eradicated without emergency vaccination, export restrictions are lifted three months after the last outbreak. With emergency vaccination it takes six months after the last outbreak or the last vaccination, depending on which was later. Serological examination has to be carried out to confirm

that no vaccinated animal is infected and to exclude the presence of carrier animals (Ganter et al., 2001; Alexandersen et al., 2002). These are persistently infected ruminants from which a live virus can be isolated at 28 days, or later, after infection (Müller et al., 2001; Grubman and Baxt, 2004) They show no clinical signs, but excrete FMDV. The role of carrier animals is still controversial as they excrete FMDV, but up to now no experimental evidence has been found that indicates that carrier cattle or sheep can transmit virus to uninfected animals (Müller et al., 2001; Alexandersen et al., 2003; Grubman and Baxt, 2004). Further research on validation of control strategies should take the existence of carrier animals into account.

Looking at the preventive culling strategy in detail shows that its efficiency has often been limited by the destruction capacity (Barnett et al., 2002; Grubman, 2005). Moreover, sufficient personnel and equipment guarantee a culling of the animals without delay. If preventive culling is applied, mostly unaffected animals are culled, e.g. for welfare reasons, such as overcrowding (Kitching et al., 2006). Ethical discussions call preventive culling politics into question and prefer a vaccination-to-live strategy to avoid the culling of unaffected animals. Cost-benefit analysis is required to compare on the one hand the direct costs of the control strategies, e.g. personnel, material, but on the other also the economical consequences of losses due to export restrictions.

Comparison of models for FMDV transmission via air

In the present study, a Fuzzy-Logic inference system for FMDV transmission by air was to be developed. It was compared to the Gaussian Dispersion model to evaluate whether Fuzzy-Logic is an appropriate technique to estimate the FMDV concentration at a certain point. Both models were observed under similar scenarios and a direct comparison of the 'real' (Gaussian Dispersion model) and simulated (FIS) output was possible. The goodness-of-fit between the models was assessed using a regression analysis described by Kleijnen et al. (1998). The sum and the difference in the corresponding output values were used in a linear regression from the sum on the difference. An F-Test was used to determine if the regression coefficients were equal to zero, indicating a sufficient model fit. Assumptions for this regression analysis were the equality of the means and variances. The present results show that the average output of both models was almost the same. Differences were observed in the variances. Extreme virus concentrations were over- and underestimated, respectively. Nevertheless, the Kleijnen Test showed an ad-

equate model fit for medium virus concentrations. Furthermore, as the test required normally distributed data, they were transformed to the logarithmic scale. Instead of a transformation, the application of bootstrapping methods was possible in further analysis (Kleijnen, 2008).

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General Summary

The aim of the present study was to develop a simulation model for the epidemiology and control of the foot and mouth disease virus (FMDV). Special emphasis was given to the modelling of airborne spread. The thesis includes the validation of the model as well as its application for the evaluation of different control strategies. Finally, a Fuzzy-Logic inference system was developed in order to generate a simple model for airborne spread including weather parameters that are easy to collect.

In Chapter One a spatial and temporal Monte-Carlo simulation model was presented that simulated the transmission of FMDV on a daily basis. The farms were located by its x-/y-coordinates and composed of sub-units, defined by their livestock. For the present analysis, a region with 729 farms in Northern Germany was assumed. Farm data were derived from the Farm Structure Survey 2003. The epidemic started with the infection of the index case and could spread via direct and indirect contacts and via the air. Contacts between farms, such as the veterinarian, animal feed vehicle and bulk milk tanker, were modelled as a routing problem, solved with the Nearest-Neighbour Algorithm. Virus transmission by wind was estimated with the Gaussian Dispersion model. The course of an infection was modelled with the infection states susceptible, infected, infectious, symptoms, diagnosed and culled. Depending on the control strategies, the additional states restricted (no movement restrictions), preventively culled, vaccinated and immune were defined. Control strategies to eradicate an epidemic were implemented according to the EU Directive (2003/85/EG): culling of infected herds, protection and surveillance zones with movement restrictions, contact tracing forward and backward, preventive culling zone and emergency vaccination.

A sensitivity analysis was performed in Chapter Two to validate the simulation model. As neither input nor output data from real epidemics were available, sensitivity analysis was a good means to test the models' robustness to changes in the input parameters. Furthermore, important influencing factors could be identified. In order to analyse a var-

ious number of influence factors and their interactions with little computational effort, a fractional factorial design was chosen. Higher-order interactions between main factors that were negligible were used to estimate other main factors. Nevertheless, two-factor interactions were considered as well. Results of the analysis were consistent with expectations and other studies. Airborne spread, the farm density in the region, the type of the index case, the control strategy and its delay of establishment showed a significant impact on the response variables, epidemic duration and mean number of infected and culled farms. Changes in the length of the routes of the veterinarian, animal feed vehicle and bulk milk tanker were of minor importance.

In the third chapter, the simulation model was applied to evaluate different control strategies with special focus on preventive culling and emergency vaccination. Different preventive culling and emergency vaccination circles were compared. Interactions with airborne spread, the farm density in the region, the type of the index case and the delay of the establishment of control strategies were taken into account. The effectivity of the control strategies was evaluated by the epidemic duration and number of infected, preventively culled and vaccinated farms. The results indicated that emergency vaccination, rapidly started in a large vaccination circle, was an alternative to preventive culling. The effectivity of preventive culling was more robust to delays in establishment. The fewest farms were infected with a combination of preventive culling and emergency vaccination within a 10 km circle, but at the expense of a high number of preventively culled and vaccinated farms. These response variables had to be considered in addition to the number of infected farms, as the application of both preventive culling and an emergency vaccination required a high amount of material and personnel resources. Larger epidemics were to be expected if the FMDV was transmitted via air, if the epidemic was located in a densely populated area or if it started on a dairy farm. Epidemics with a FMDV that is highly transmissible via air were more severe if they started on a pig farm than on a dairy farm. Without the possibility of airborne spread, dairy farms were the higher risk.

Finally in Chapter Four, a Fuzzy-Logic inference system (FIS) for airborne spread was developed and compared to the Gaussian Dispersion model. The virus concentration at a certain point was to be estimated, depending on weather conditions, amount of virus excretion and the distance to the source. Real weather data recorded in Vienna, Austria, were used to evaluate whether the Fuzzy-Logic method was an adequate modelling technique for airborne spread. The mean output of the FIS was almost identical to the

Gaussian Dispersion models' output, but the variances were different. Low and high virus concentration were under- and overestimated, respectively. The input parameters, membership functions and rules for the FIS needed a further adjustment to increase the variance in the values and to allow a more accurate estimation of extreme virus concentrations.

Zusammenfassung

Die vorliegende Arbeit hat das Ziel ein Modell zu entwickeln, dass die Ausbreitung und Bekämpfung des Maul- und Klauenseuche Virus (MKSV) abbildet. Durch die Entwicklung eines räumlichen und temporären Monte-Carlo-Simulationsmodells ist es möglich die Effektivität verschiedener Bekämpfungsmaßnahmen, insbesondere der präventiven Keulung und Notimpfung, zu vergleichen und Interaktionen mit weiteren Faktoren zu berücksichtigen. Darüber hinaus wird die Anwendung von Fuzzy-Logik für die Modellierung der Virusausbreitung per Luft evaluiert.

Im ersten Kapitel wird das Simulationsmodell beschrieben, welches auf Tages- und Betriebsbasis das jeweilige Seuchengeschehen berechnet. Die Datengrundlage für die untersuchten Szenarien bilden 729 Betriebe aus Norddeutschland, die über die Agrarstrukturdatenerhebung von 2003 erfasst wurden. Jeder Betrieb wird über seine x- und y-Koordinate lokalisiert und besteht aus verschiedenen Untereinheiten, die durch die Art der Tiere definiert werden. Eine Epidemie beginnt mit der Infektion des Indexbetriebes und breitet sich durch direkte Tierkontakte, indirekte Personen- und Fahrzeugkontakte und über die Luft aus. Die indirekten Kontakte über den Tierarzt, Futtermittelfahrzeuge und den Milchsammelwagen werden als Tourenproblem abgebildet und mithilfe des Nearest-Neighbour Algorithmus berechnet. Ein integriertes Gaußmodell schätzt die Ausbreitung des MKSV über die Luft. Die Bekämpfungsmaßnahmen wurden in Anlehnung an die EU Richtlinie (2003/85/EG) implementiert. Hierzu zählen die Einrichtung eines Sperrbezirks und Beobachtungsgebietes sowie die präventive Keulung, Kontaktrückverfolgung und Notimpfung.

Eine Sensitivitätsanalyse des Simulationsmodells erfolgt in Kapitel 2. Bei Abwesenheit realer Input- und Outputdaten, kann eine Sensitivitätsanalyse angewendet werden, um die Robustheit des Modells gegenüber Veränderungen in den Inputparametern zu untersuchen. Außerdem können wichtige Einflussfaktoren bestimmt werden. Ein fraktioniert faktorielles Design erlaubt die Schätzung vieler Faktoren und gleichzeitig die Be-

grenzung des Rechenaufwands. Mit Hilfe der Outputparameter Epidemiedauer sowie der Anzahl der infizierten und gekeulten Betriebe werden die verschiedenen Szenarien verglichen. Die Faktoren Luftausbreitung, Betriebsdichte, Art des Indexbetriebes, wie auch die Bekämpfungsstrategie und die zeitliche Verzögerung bis diese implementiert wurde, beeinflussen das Ergebnis der Simulation signifikant. Im Gegensatz dazu hat die Tourenlänge des Tierarztes, des Futtermittelfahrzeuges und des Milchsammelwagens nur einen geringen Einfluss.

Im dritten Kapitel werden verschiedene Bekämpfungsmaßnahmen, insbesondere die präventive Keulung und die Notimpfung, verglichen. Weiterhin finden Interaktionen mit der Luftausbreitung, der Betriebsdichte, dem Typ des Indexbetriebes und der Verzögerung bis zum Beginn der Bekämpfungsmaßnahme Berücksichtigung. Die Epidemiedauer sowie die Anzahl der infizierten, präventiv gekeulten und geimpften Betriebe werden zur Evaluation herangezogen. Die Ergebnisse zeigen, dass die Notimpfung eine Alternative zur präventiven Keulung darstellt, wenn diese ohne Verzögerung und in einem großen Radius angewendet wird. Im Hinblick auf die Beständigkeit der Effektivität erweist sich die präventive Keulung als stabiler. Die Kombination von präventiver Keulung und Notimpfung führt zu der geringsten Anzahl infizierter Betriebe. Allerdings hat diese Verknüpfung eine hohe Anzahl präventiv gekeulter und geimpfter Betriebe zur Folge. Engpässe bei der Verfügbarkeit von Personal und Material können die Durchführung und damit die Effektivität dieser kombinierten Bekämpfungsmaßnahme begrenzen. Die Virusausbreitung über die Luft hat ebenfalls einen signifikanten Einfluss auf die Anzahl infizierter Betriebe. Die Interaktion zwischen Luftausbreitung und Indexbetrieb zeigt, dass ein Schweinebetrieb als Initiator, im Gegensatz zu einem Milchviehbetrieb, zu einer größeren Epidemie führt, wenn die Ausbreitung über die Luft möglich ist. Ist eine Luftübertragung des MKSV allerdings nicht möglich, so nimmt eine von einem Milchviehbetrieb ausgehende Epidemie größere Ausmaße an, als wenn der Indexbetrieb Schweine halten würde.

Im vierten Kapitel wird die Anwendung von Fuzzy-Logik für die Schätzung der Luftausbreitung von MKSV beschrieben. Ziel war es ein einfaches Fuzzy-Logik Inferenz System (FIS) mit leicht erfassbaren Parametern zu entwickeln. Reale Wetterdaten aus Wien werden sowohl für das FIS als auch für ein Gaußmodell, das als Referenzsystem dient, herangezogen. Es zeigt sich, dass die Modellierung der Luftausbreitung mittels Fuzzy-Logik möglich ist. Die mittlere geschätzte Viruskonzentration war für die beiden Modelle

identisch, wobei extreme Viruskonzentrationen jeweils unterschätzt bzw. überschätzt wurden. In weiteren Analysen ist eine Modifikation der Inputparameter notwendig, um eine genauere Schätzung extremer Konzentrationen zu ermöglichen.

Danksagung

An dieser Stelle möchte ich mich bei allen Menschen bedanken, die zur Umsetzung und zum Gelingen dieser Arbeit beigetragen haben.

Herrn Prof. Dr. J. Krieter danke ich sehr für die Überlassung des interessanten Themas, die wissenschaftliche Betreuung, die mir gewährleisteten Freiräume bei der Erstellung der Arbeit sowie die Möglichkeiten, meine Ergebnisse auf Tagungen im In- und Ausland zu präsentieren.

Herrn Prof. Dr. G. Thaller danke ich für die Übernahme des Koreferates.

Bei Herrn Dr. J. Teuffert vom Friedrich-Loeffler-Institut in Wusterhausen bedanke ich mich für die ständige Hilfsbereitschaft und die fachliche Unterstützung bei allen epidemiologischen Fragestellungen.

Bei Herrn Dr. G. Rave aus dem Institut für Variationsstatistik bedanke ich mich für die Anregungen und die Hilfe bei den statistischen Auswertungen.

Für die finanzielle Unterstützung danke ich der Uelzener Allgemeinen Versicherungsgesellschaft a.G., VGH Versicherungen, Westfälische Provinzial Versicherung, Bayerischer Versicherungsverband und der Landwirtschaftlichen Rentenbank.

Darüber hinaus möchte ich mich bei allen Kollegen für die schöne Zeit am Institut bedanken. Mein besonderer Dank gilt allen aktuellen und ehemaligen "Containermitbewohnern", insbesondere Tanja, Lotti und Diane für die tollen Erlebnisse vor, während und nach der täglichen Arbeit.

Mein größter Dank gilt meiner Familie, meinen Freunden und besonders meinem Mann Claus. In jeder Phase meiner Doktorandenzeit habt Ihr an mich geglaubt, mir geholfen und mich bei allem unterstützt.

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