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A metapopulation model for the spread and persistence of contagious bovine pleuropneumonia (CBPP) in African sedentary mixed crop-livestock systems

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Abstract (226 words)

Contagious bovine pleuro-pneumonia (CBPP) is endemic in several developing countries. Our objective is to evaluate the regional CBPP spread and persistence in a mixed crop-livestock system in Africa. A stochastic compartmental model in metapopulation is used, in which between-herd animal movements and the within-herd infection dynamics are explicitly represented. Hundred herds of varying size are modelled, each sending animals to $n$ other herds (network degree). Animals are susceptible, latent, infectious, chronic carrier or resistant. The role of chronic carriers in CBPP spread being still debated, several chronic periods and infectiousness are tested. A sensitivity analysis is performed to evaluate the influence on model outputs of these parameters and of pathogen virulence, between-herd movement rate, network degree, and calves recruitment. Model outputs are the probability that individual- and group-level reproductive numbers $R_0$ and $R^*$ are above one, the metapopulation infection duration, the probability of CBPP endemicity (when CBPP persists over five years), and the epidemic size in infected herds and infected animals. The most influential parameters are related to chronic carriers (infectiousness and chronic period), pathogen virulence, and recruitment rate. When assuming no CBPP re-introduction in the region, endemicity is only probable if chronic carriers are assumed infectious for at least one year and to shed the pathogen in not too low an amount. It becomes highly probable when assuming high pathogen virulence and high recruitment rate.

Keywords: Epidemic model; Network; Sensitivity Analysis; Disease Endemicity; Chronic Carrier
1. Introduction

Contagious bovine pleuropneumonia (CBPP) is a respiratory disease of cattle caused by *Mycoplasma mycoides* subsp. *mycoides* small colony (*MmmSC*) (Cottey and Yeats, 1978; Nicholas and Bashidurin, 1995). A former ‘list-A’ disease of World Organisation for Animal Health (OIE) (Lefèvre, 2000; OIE, 2003), CBPP is a major concern for numerous developing countries (because of livestock mortality and production losses and disease control costs). For example, the Pan African programme for the Control of Epizooties (PACE) (this programme was implemented by the African Union Interafrican Bureau for Animal Resources [AU-IBAR] in 32 African countries and was principally funded by the European Commission with the support of the participating African countries) has identified CBPP as the second most important transboundary disease in Africa after rinderpest (Tambi et al., 2006).

Contagion occurs through direct and repeated contacts between infected and susceptible cattle, essentially through expectorations of coughing animals (Nicholas and Bashidurin, 1995; Provost et al., 1987). Cattle movements (social or contractual loaning, purchases and sales of animals in local markets) are the main risk of between-herd CBPP spread in that farming system (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et al., 2002a). CBPP shows a large range of severity and signs (Provost et al., 1987). Some animals appear to be naturally resistant. Subclinical forms are frequent. Severe respiratory signs are the most–prominent features observed in the clinical cases, and are associated with typical lesions of pleurisy and pneumonia. Recovered cattle often have necrotic lung tissue, encapsulated in sequestra where mycoplasmas can survive. The involvement of chronic carriers in the perpetuation of the infection has been suggested by several authors (Egwu et al., 1996; Mahoney, 1954; Martel et al.,
It is still debated since carriers’ infectivity has not been demonstrated yet. For example, Windsor and Masiga (1977) did not observe CBPP transmission after challenging experimentally susceptible animals with chronic carriers. CBPP outbreaks have essentially been described at the herd level, in experimental (Hudson and Turner, 1963; Thiaucourt et al., 2000; Yaya et al., 1999) or natural conditions (Bygrave et al., 1968; Lesnoff et al., 2004b). Nevertheless, the threat in African countries goes beyond the individual farms and need to be evaluated at a higher level (an infected herd is a risk for neighbouring herds due to frequent and uncontrolled animal movements). CBPP outbreaks in a farmers community, in a village or in a region are unfortunately much more complex to quantify and poorly documented (at the knowledge of the authors, no incidence data are available).

For better understanding the CBPP persistence in a region and being able to evaluate the impact of different control strategies at this level (e.g. vaccinations or treatments and isolation of seek animals), it is necessary to develop dynamics models. A CBPP spread metapopulation model was already developed for representing three connected large-size (≥ 50 to more than 3,000 animals) mobile herds of a pastoral community in East Africa (Mariner et al., 2006). We propose a metapopulation model for a sedentary mixed crop-livestock system, composed of a larger number of herds, sedentary and of small size.

Within a small herd, it has been shown that CBPP cannot persist if infected animals are not re-introduced or if chronic carriers are not involved in the transmission dynamics (Lesnoff et al., 2004a). However, spatial heterogeneity due to the structure of the population (here the farming system structured into herds) influences disease persistence and dynamics (Ball et al. 1997). Asynchrony in disease dynamics may arise
among herds within a region, allowing a global persistence of a disease because of a ‘rescue effect’: moving infected animals may reintroduce the disease in herds where it has locally died out (Grenfell and Harwood, 1997; Lloyd and May, 1996). In such a context, the disease may persist in the metapopulation of herds (or the infection duration of the metapopulation may be longer than in a single herd) without the need of disease re-introductions or without assuming any role played by CBPP chronic carriers in the disease spread.

In the present paper, a stochastic compartmental model is developed for studying the spread and persistence of CBPP in a newly infected area, representing a hypothetic metapopulation of sedentary herds in a mixed-crop livestock farming system. No CBPP re-introduction or control interventions are assumed in the area (such as vaccination, animal isolation and slaughtering, or chemotherapy). The objective is to identify the most influential parameters on the invasion threshold at the metapopulation level, on the infection duration and the probability of CBPP endemicity (disease persistence over more than 5 years) in a bovine metapopulation, and on the epidemic size at the herd and at the individual levels. To fulfil this objective, we analyse the sensitivity of these model outputs to variations in model parameters, and especially parameters generally influencing disease spread and persistence (level of recruitment, pathogen virulence, between-herd animal movement, and network degree) and parameters with uncertain values (shedding period and infectiousness of chronic carriers).

2. Model framework

The model is compartmental, stochastic and uses discrete time with a time interval of one week. The metapopulation consists in a set of herds exchanging animals. The model
explicitly represents the within-herd CBPP dynamics and the between-herd animal
movements. A simulation consists in several repetitions of CBPP spread in the
metapopulation over a defined time interval.

2.1 Within-herd spread of CBPP

The within-herd model is adapted from different models developed in a research project
in the Ethiopian highlands (Balenghien et al., 2004; Lesnoff et al., 2002b, 2004a and
2004c) and is briefly described thereafter (Fig. 1).

The model represents managed open herds of cattle with entries in and exits from the
herds. All the within-herd model parameters are described in Tab. 1. Young animals
(< 6 months) are not represented because they are more resistant to CBPP than adults
are. They are assumed not contributing to the spread of the disease (Curasson, 1942;
Provost et al., 1987). The natural recruitment rate among animals born in the herd
corresponds to the birth rate times the probability of still being in the herd six months
after birth. A proportion $p_{m}$ of recruited animals are naturally resistant to infection,
other being susceptible. In addition, animals not born in the herd may also enter the herd
(e.g. by purchases, gifts or contractual loans). Exits correspond to deaths and living
animals that leave the herd (sales, slaughtering or contractual loans).

In herd $x$, animals can be of five infection states: susceptible ($S_x$), incubating (infected
but not yet infectious) ($E_x$), infectious ($I_x$), chronically infected (not or slightly
infectious; $Q_x$), and recovered (immunised) or naturally resistant to infection (not
infectious; $R_x$). Consistent durations in states $E$, $I$, and $Q$ are assumed (Tab. 1). CBPP
transmission between animals is density-dependent. Infectious individuals have a
disease-related mortality, which largely increases with pathogen virulence (Tab. 1).
Transitions between infection-states, deaths and movements due to the sell-and-purchase process are simulated from multinomial random generators that allow taking into account of possible disease fade-outs, characteristics of small populations (Anderson and May, 1991) (Tab. 2).

2.2 Between-herd spread of CBPP

A metapopulation of \( N \) cattle herds representing a typical sedentary mixed crop-livestock area is modelled. Herds are of various sizes, ranging from 1 to 40 animals with 8 animals on average. This represents the observed heterogeneity among this kind of system (e.g. Bonnet et al., 2005; Lesnoff et al., 2002a). Each herd is connected to exactly \( n \) other herds (corresponding to the network degree) in which it can eventually send animals. For each realisation of the model, \( n \) herds are randomly chosen for each herd among the \( N-1 \) possible herds before the initial introduction of the disease in the area.

Among animals leaving herd \( x \) (on average \( \pi Z_x \) animals for a movement rate from the herd \( \pi \) and infection-state \( Z \), where \( Z_x \) is the number of animals of state \( Z \) in herd \( x \)), a proportion \( p_{in} \) stays in the modelled area, i.e. move from herd \( x \) to one of the \( n \) herds connected to \( x \). This proportion has been adjusted to ensure the demographic equilibrium of the metapopulation (i.e. on average the metapopulation size is consistent over time). The destination of each movement is randomly chosen among the \( n \) herds with a uniform probability. Hence, each of these \( n \) herds has a chance \( 1/n \) to be chosen for each movement. Any other probability distribution could be used if information was available about preferences that may exist towards a given herd among all potential...
source herds. Assuming a uniform probability for this choice, the average number of
animals of state $Z$ entering herd $x$ is:

\[
\Omega(Z_x) = \sum_{i=1}^{j=T} p_{in} \pi Z_i \frac{\sigma_{ix}}{\sum_{j=1}^{i=T} p_{in} \pi Z_j} = \sum_{i=1}^{j=T} p_{in} \pi Z_i \frac{\sigma_{ix}}{n},
\]

with $\sigma_{ij} = 1$ if herd $j$ is part of the $n$ herds of destination of herd $i$, 0 otherwise (see Tab. 1 for a definition of other parameters). Animals entering herd $x$ (purchases, loans, etc.) can be of any infection-state ($S$, $E$, $I$, $Q$, $R$). No neighbouring relationships, as for example contacts at pasture, is modelled (animals movements are considered as the only cause of between-herd infection).

### 2.3 Scenarios

Scenarios are defined based on different levels of chronic carriers infectiousness $\beta_Q$ and shedding period duration $d_Q$, of pathogen virulence (varying both the transmission rate $\beta_I$ and the disease-related mortality of infectious animals $\alpha$ in status $I$), of within-herd calves recruitment rate, of the network degree of the metapopulation, and of between-herd animal movements.

The infectiousness and the shedding period of chronic carriers are debated and the corresponding parameters values remain fully uncertain. Four levels of $\beta_Q$ (all far lower than infectiousness of animals in state $I$; Tab. 3) and two values of $d_Q$ (26 and 52 weeks) are tested. Moreover, in the literature, variable levels of virulence (in terms of incidence and disease-related mortality) have been reported (Masiga et al., 1996; Provost et al., 1987). In the article, two levels of pathogen virulence are tested: low-virulence ($LVIR$) vs. high-virulence ($HVIR$) (Tab. 3).
Although they are known to influence the spread of pathogens in structured populations (Keeling and Eames, 2005; Kiss et al., 2006; Vincente et al., 2007), the recruitment rate, the between-herd contact structure, and the associated animal movement rate depend on the situation and on the farming system. Three recruitment rates, three network degrees (represented by the number of herds to which a herd is connected and to which it can send animals; the highest degree corresponds to a complete network, all herds being in contact with each other) and two movement rates are tested (Tab. 3).

A full factorial design is built by combining all the levels of the six variation factors, resulting in 288 scenarios. For each scenario, 200 realisations are performed over a 10-year simulation period. The number of realisations is a compromise between steady output distributions and simulation time. Five incubating animals are initially introduced in randomly chosen herds of the metapopulation. The metapopulation consists in \( N = 100 \) herds. No re-introduction of the disease is allowed.

### 2.4 Output

Three indicators of the disease spread and persistence are evaluated. First, the proportions of model realisations with a simulated animal-level \( (R_0) \) and group-level \( (R^*; \text{Ball et al. 1997}) \) reproductive numbers above one are evaluated (denoted thereafter by \( P(R_0 > 1) \) and \( P(R^* > 1) \) respectively; Tab. 4). The more extensively used basic reproductive number \( (R_0) \) has been extended in multiple ways to account for example for depletion in susceptible individuals (Keeling and Grenfell, 2000) or for population structure (Keeling, 1999; Fulford et al., 2002). However, \( R_0 \), which is an individual-based criteria, is less appropriate to predict disease invasion in a metapopulation framework than the group-level reproductive number \( R^* \), as
demonstrated using a phenomenological mixing model (Ball et al., 1997; Ball, 1999; Ball and Lyne, 2001; Ball and Neal, 2002) or a mechanistic mixing model (Cross et al. 2005, 2007). In the present article, $R_0$ and $R^*$ are simulated for each realisation of the model. Initially, a single animal in state $E$ (index case) is introduced in a randomly chosen herd (index herd). The herds forming the metapopulation have a uniform probability of being chosen and this choice is made independently for each model realisation. All other animals in the metapopulation are initially either susceptible (proportion $1 - \text{pres}$) or naturally resistant (proportion $\text{pres}$). On the one hand, $R_0$ is calculated as the number of newly infected animals (leaving state $S$ because of infection) in the metapopulation caused by the index case over its lifetime, this individual being allowed to move between herds. Newly infected animals can infect animals as soon as infectious, resulting in a local depletion in susceptible animals available for infection by the index case. On the other hand, $R^*$ is calculated as the number of newly infected herds in the metapopulation due to movements of infected individuals from the index herd over its infection duration (Cross et al., 2005). Animals in newly infected herds can infect animals as soon as infectious. This results in decreasing the number of susceptible animals available for infected animals from the index herd. As simulated with the model, these estimates of $R_0$ and $R^*$ account for the population structure, animal movements, and the depletion in susceptible animals, and thus differ from traditional analytical values, which assume an infinite susceptible population.

Second, the infection duration of the metapopulation is evaluated for each model realisation, and denoted thereafter by $\text{InfDur}$ (Tab. 4). When chronic carriers are assumed not infectious, the metapopulation is considered to be infected as long as at
least one animal in state \( E \) or \( I \) is still present. When chronic carriers are assumed infectious, the metapopulation is considered to be infected as long as at least one animal in state \( E, I, \) or \( Q \) is still present. The average duration and the associated standard error are calculated. Moreover, we define CBPP to be endemic when it persists over more than five years. Hence, the probability of endemicity (denoted by \( P(\text{endemic}) \), Tab. 4) is calculated as the proportion of realisations in which the infection duration is above five years.

Third, the epidemic sizes at both the individual and the herd levels are evaluated, i.e. the cumulative incidence in infected individuals (herds, respectively) over the simulation period. The epidemic size at the individual level is the cumulative number of animals newly in state \( E \) in the metapopulation. A herd is considered to have been infected over the simulation period if an animal in state \( E \) or \( I \) (or also in state \( Q \) in scenarios assuming chronic carriers to be infectious) had belonged at least for one time interval to the herd. Epidemic sizes are denoted thereafter by \( \text{EpSiz}(I) \) and \( \text{EpSiz}(H) \) and for the individual and the herd levels respectively (Tab. 4).

3. Sensitivity analysis

Based on the model realisations implemented in the full factorial design, the contributions of the variation factors to the outputs variability are evaluated using a linear regression approach (Saltelli et al., 2000). For each output, a linear regression model is fitted with all the principal effects of the factors and their first-order interactions. A minimum variance criterion is defined: factors or interactions accounting for more than 1% of variance are retained in the model. The global contribution of
factor $i$ (including the principal effect plus interactions in which factor $i$ is involved) to
the variation in output $y$ is:

$$
C_i^y = \frac{SS_i^y + \frac{1}{2} \sum_j SS_{i:j}^y}{SS_{tot}^y},
$$

with $SS_{tot}^y$ the total sum of squares of the model for output $y$, $SS_i^y$ the sum of squares
related to the principal effect for factor $i$ for output $y$ (nil if factor $i$ is not retained in the
model), $SS_{i:j}^y$ the sum of squares related to the interaction between factor $i$ and factor $j$
for output $y$ (nil if this interaction is not retained in the model). The sum of the
contributions for output $y$ equals the coefficient of determination of the regression
model $R^2$. In the article, the sensitivity of the outputs is then analysed only in relation to
factors contributing the most to their variations.

4. Results

4.1 Factors contributing to variation in model output

The factors contributing the most to the model output variations are the parameters
related to chronic carrier animals ($\beta_Q$ and $d_Q$), the pathogen virulence, and the
recruitment rate (Fig. 2). The movement rate and the network degree only contribute to
the variation in $P(R* > 1)$.

Depending on the outputs, the most contributing parameters explain all together from
52% to 95% of the variance. $\beta_Q$ and $d_Q$ are highly influential, explaining together from
26 to 66% of the output variance. Pathogen virulence explains from 10 to 18% of the
output variance, except for $P(R0 > 1)$ for which it is with $\beta_Q$ the most influent parameter.
Calves recruitment explains from 0 to 15% of the output variance, contributing essentially to the variation in $P(\text{endemic})$, $EpSiz(I)$ and $EpSiz(H)$.

4.2 Reproductive numbers at the metapopulation level

$R_0$ shows different patterns depending on LVIR or HVIR scenarios. In LVIR, the average $R_0$ and $P(R0>1)$ are always below 1 and 30% respectively, $P(R0>1)$ only slightly increasing with $\beta_Q$ and $d_Q$ (Fig. 3). In HVIR, however, the average $R_0$ is above one, even when $\beta_Q = 0$. $P(R0>1)$ ranges from 24 to 65% (Fig. 3) with a net influence of chronic parameters (although levels $\beta_Q = 0$ and $\beta_Q = \beta_I/1000$ show similar results).

In contrast, $R^*$ shows low values for both LVIR and HVIR. In all scenarios, the average $R^*$ and $P(R^*>1)$ are below one and 20% respectively. This shows that under the tested range of parameters’ values it is difficult for the disease to invade the metapopulation.

In LVIR, $P(R^*>1)$ is even below 5% and always nil when $\beta_Q = 0$ (Fig. 4a). In HVIR, $P(R^*>1)$ clearly increases with $\beta_Q$, $d_Q$, and the movement rate (Fig. 4b).

As indicated in Fig. 2, the network degree also contributes to $P(R^*>1)$. $P(R^*>1)$ is positively correlated to this parameter, but only when $\beta_Q = \beta_I/100$ or $\beta_Q = \beta_I/50$ (patterns are not clear for lower chronic infectiousness).

4.3 Duration of the metapopulation infection and probability of endemicity

$\beta_Q$, $d_Q$, pathogen virulence, and recruitment rate are the parameters influencing the most $\text{InfDur}$. In all scenarios, average $\text{InfDur}$ is shorter than 6 months when chronic carriers are assumed not infectious (Fig. 5). The longest average $\text{InfDur}$ in LVIR and HVIR are above 4 and 8 years, observed with $\beta_Q = \beta_I/50$, $d_Q = 52$ weeks and a high recruitment rate. By model construction, $\text{InfDur}$ increases with $d_Q$ when $\beta_Q > 0$ (Fig. 5).
Nevertheless, whereas $d_Q$ is doubled (26 to 52 weeks), average $InfDur$ is tripled for $\beta_Q = \beta_i/50$ and a high recruitment rate. The recruitment rate increases average $InfDur$ but essentially when $\beta_Q = \beta_i/100$ or $\beta_i/50$ and $d_Q = 52$ weeks.

Concerning CBPP endemicity, $P(\text{endemic})$ is nil when $d_Q = 26$ weeks, and when $d_Q = 52$ weeks and $\beta_Q = 0$ or $\beta_i/1000$. In other situations, $P(\text{endemic})$ is highly sensitive to $\beta_Q$, pathogen virulence, and recruitment rate (Fig. 6). Endemicity becomes highly probable ($P(\text{endemic}) > 0.50$) when assuming a high recruitment rate in HVIR.

**4.4 Epidemic size in infected herds and in infected individuals**

When $d_Q = 26$ weeks, average $EpSiz(H)$ only varied from 5 to 8% of the herds depending on the other variation factors considered (Fig. 7). The infected herds correspond mostly to the initially infected herds (five infected animals are introduced initially in randomly chosen herds in a metapopulation of 100 herds). When $d_Q = 52$ weeks, average $EpSiz(H)$ shows a higher variability and increases with $\beta_Q$, the pathogen virulence, and the recruitment rate (Fig. 7). Nevertheless, average $EpSiz(H)$ remains lower than 15% in all LVIR scenarios, and in HVIR overpasses 20% only for $\beta_Q = \beta_i/100$ or $\beta_i/50$ with a high recruitment rate.

The same kind of results are found for average $EpSiz(I)$, but with a higher sensitivity to variation factors (even when $d_Q = 26$ weeks) (Fig. 8) since $EpSiz(I)$ results from within-herd infection that can spread at least in the initially infected herds.

For both $EpSiz(H)$ and $EpSiz(I)$, the model shows few differences between scenarios assuming no vs. a low infectiousness of the chronic carriers (Fig. 7 and 8).

5. Discussion
Endemicity of CBPP is assumed in several regions of Africa, among which regions with mixed crop-livestock systems (FAO, 2003). The proposed model has been developed to represent the spread of CBPP between cattle herds in a mixed crop-livestock farming system and to evaluate if the disease could be endemic in a (originally CBPP free and naïve) metapopulation of herds assuming no disease re-introduction. In our simulations and based on the scenarios considered, infectiousness and shedding period duration of chronic carriers, pathogen virulence, and calving recruitment rate are the most influential factors on the probability for CBPP to invade the metapopulation, the CBPP endemicity and the infection sizes. In contrast, although diseases are known to generally better persist in heterogeneous populations (Lloyd and May, 1996), the between-herd movement rate and the network degree linking the herds do not influence significantly the model outputs, except $P(R^* > 1)$. One important result is that CBPP endemicity as defined in our model (and assuming no disease re-introduction) is only probable if chronic carriers are assumed infectious for a long period of time (one year in the article) and to shed the pathogen in not too low an amount. It becomes highly probable when assuming and a high pathogen virulence and a high level of recruitment. This demonstrates that chronic carriers, if infectious, are a possible determinant of CBPP persistence in African sedentary farming systems. Nevertheless, the ability of chronics carriers to transmit the disease has still never been proved (Windsor and Masiga, 1977). Recent experimental studies (Huebschle et al., 2006a,b) showed that CBPP seek animals treated with antibiotics and surviving to the disease (similarly to naturally chronics carriers) can remain infectious. However, infectiousness is mitigated compared to untreated and seek animals. Another obvious possible determinant of CBPP persistence is the regular re-introduction of seek animals from other endemic regions,
reproducing a source-sink process. More biological researches on the evaluation of the infectiousness of chronic carriers are needed for prioritising one of these two hypotheses.

The probability for a disease to invade a metapopulation has been shown to be better understood at the patch-level than at the individual-level (Ball and Neal, 2002). A group-level reproductive number has been introduced as an indicator of the capability of a pathogen to invade a human population partitioned in many small households (Ball et al., 1997; Ball, 1999; Ball and Lyne, 2001; Ball and Neal, 2002). It has been extended to the case of a structured population with explicit movements of individuals (mechanistic metapopulation model) and compared to $R_0$ (Cross et al., 2005, 2007). Our results are coherent with expectations: the probability of having newly infected individuals is mainly influenced by the transmission rates (i.e. what happens at a local scale), whereas the probability of having new herds infected is also influenced by the movement rate and the network degree (Cross et al., 2007). However, the movement rate and the network degree do not influence other model outputs. Here, the network degree should be highly related to the herd epidemic size, as the highest number of herds that can be infected per infected herd equals the network degree. However, CBPP spreads very slowly in the metapopulation and each herd contributes to a very low number of newly infected herds (average $R^* < 1$, whatever the network degree). As a result, the network degree – even if low – does not constrain the spread of the disease here and we do not observe a maximum in CBPP persistence for intermediate level of coupling (Keeling and Eames, 2005). As pointed out by Cross et al. (2005), chronic diseases, with a longer infectious period and thus more between-herd movements of
infected animals over the infectious period, may perceive a structured population as an homogeneous one. In contrast, when assuming chronic carriers not to be infectious, the population structure has a strong impact on CBPP spread and persistence, the movement rate being too low to enable CBPP endemicity (Jesse et al., submitted).

The proposed stochastic model includes a compartmental model of the within-herd spread of CBPP, adapted from models developed in a research project in the Ethiopian highlands (Balenghien et al., 2004; Lesnoff et al., 2002b, 2004a and 2004c). A metapopulation approach has been used to extend the within-herd model to a regional infection dynamics. The modelled region is a population of herds of different sizes. The within-herd infection dynamics is explicitly represented, as well as animal movements between herds, known as a main source of CBPP regional spread in sedentary mixed crop-livestock systems (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et al., 2002a). All the model parameters have a biological meaning and can be estimated from field data or experiment (basically from within-herd incidences and animal exchange rates). For example, the present model has been calibrated using longitudinal data on naturally and newly CBPP-infected herds obtained from a follow-up survey formerly implemented in Ethiopia in small and sedentary herds of mixed crop-livestock systems (Lesnoff et al., 2002a, 2004b).

In the literature, three general approaches have been used to model the regional spread of a pathogen in a metapopulation of herds. In the first approach, both the metapopulation structure and the variability in the within-herd disease spread are modelled (Ball et al. 1997; Cross et al. 2005; Hess, 1994, 1996; Swinton et al., 1998;
Vazquez, 2007), as proposed in the present model. A second approach accounts for the metapopulation structure but without representing the within-herd spread of the disease. This approach has been frequently used to model the spread of highly contagious diseases (e.g. for applications to classical swine fever: Mangen et al., 2002; to foot-and-mouth disease: Le Menach et al., 2005; to avian influenza: Le Menach et al., 2006), because the within-herd prevalence quickly reaches equilibrium for such diseases. For example in foot-and-mouth disease, 90% of the animals in a herd become infected in less than a week on average after a primary infection occurs (Le Menach et al., 2005), i.e. in each infected herd prevalence predictably and rapidly rises to 90%. This second approach has also been used to model disease spread in wildlife metapopulation (Hess, 1996; Gog et al., 2002; McCallum et al., 2002), and more recently to model the spread of Salmonella between cattle herds (Xiao et al., 2007). A third approach assumes the region as a unique population. In this approach, the evolution in individual infection statuses (e.g. SEIR) is modelled without representing the structure of the host metapopulation (e.g. in a vector-borne disease: Tran and Raffy, 2006; in an air-borne disease for the animal reservoir: Iwami et al., 2007).

Although the last two approaches are far simpler than the first one, they are inadequate when modelling the spread of CBPP in mixed crop-livestock systems in Africa. On the one hand, the within-herd CBPP spread is too slow to be neglected as it is done in other diseases. The within-herd CBPP prevalence (and therefore the contribution of herds to the outbreak) vary over time and among infected herds and the epidemiological structure does not reach quickly a consistent equilibrium, which is needed to neglect the within-herd disease spread in the metapopulation model. On the other hand, an average transmission rate for a homogeneous region cannot be estimated because of – as far as
we know – a lack of animal-level incidence data at the regional scale in mixed crop-
livestock systems in Africa. The within-herd transmission rate cannot be used because
the regional transmission rate is expected to be far lower than this local transmission
rate. Moreover, an average regional model assumes a homogeneous mixing between
animals in the region, whereas animals are structured into herds in the field. A model of
CBPP spread in a pastoral area has been proposed in which three very large herds were
considered (Mariner et al., 2006). In this model, both the within- and the between-herd
CBPP spread were represented. The between-herd spread was modelled using a
between-herd transmission rate, resulting in a need to estimate this global transmission
rate. In contrast, in the proposed model CBPP infection dynamics are modelled at the
within-herd scale (for which data are available to estimate the infection parameters) and
the between-herd spread is mechanistically modelled, in relation with animal
movements which are explicitly modelled and which can be quantified in the field. This
is an original approach to model the between-herd spread of CBPP.

The representation of between-population individual movements is of particular interest
in studying the epidemiology of long-lasting diseases. In human epidemiology,
individual movements are generally “go-and-return” like. Most of the movements are
then visits of short duration compared to the infection duration. In that context,
modelling explicit movements (mechanistic approach) or using a phenomenological
formulation was found to be almost equivalent (Keeling and Rohani, 2002). In animal
epidemiology, however, individual movements are generally of the type “go-without-
return” (sales or purchases) or long lasting visits (loans that can last for several months).
Hence, the mechanistic approach used in our model seems here more appropriate.
The heterogeneity in herd sizes induces variations in the within-herd spread of CBPP among infected herds and therefore in the risk of between-herd infection and in the global dynamics. Representing this heterogeneity, as for example in our mechanistic metapopulation model, is an interesting extension of previous disease dynamics models. Nevertheless, one main difficulty is to model the contact rate and the within-herd transmission rate. In the present model, we assume that herds are small enough (herd sizes range from 1 to 40 animals as observed in the field; Bonnet et al., 2005; Lesnoff et al., 2002a) to consider that the contact rate between animals increases linearly with herd size and that the within-herd force of infection is density-dependent (McCallum et al., 2001). In systems with larger herds, however, the contact rate may reach a saturation threshold and the density-dependent assumption for the within-herd force of infection may not be adequate. For example, cattle herds in pastoral areas may be so large that the number of contacts between animals is constant whatever the herd size, the probability of contact with an infectious animals being thus frequency-dependent (McCallum et al., 2001). If the assumption about the force of infection changes, the within-herd transmission rate should be re-estimated per herd size class or to be an explicit function of the herd size. Such questions were not under the scope of the present article and were not explored but are interesting perspectives.

In mixed crop-livestock systems, relationships between neighbouring herds other than animal movements are not the main factor of between-herd spread (Bonnet et al., 2005; Laval and Workalemahu, 2002; Lesnoff et al., 2002a). Here, animal movements are not related to the distance between herds since the modelled area is small. In that situation,
random exchanges are realistic. Qualitative observations on the field indicate that – on the modelled scale – a farmer can exchange animals with a farm located at either 100m or 5km from his farm with the same probability, exchanges being at this scale more related to local opportunities and social relationships. If a larger region was to be modelled, then the distance between herds may influence animal exchanges. Moreover, for the model to be general and to take into account all known risk factors such as animal divagation, neighbouring relationships should be further added to the model. Research is needed to account for space in the modelled network.

Finally, the proposed model is sufficiently generic to be adapted to other directly transmitted diseases with a SEIR infection dynamics and for which the main risk factor of regional spread is individual movements. The only constraint is to estimate the model parameters: the within-herd force of infection, the range of herd sizes for which this force of infection applies and the movement rates. From a practical point of view, our model can help in the future in identifying control measures for preventing or reducing the herd- and animal-level CBPP prevalence in a region (such as vaccinations, chemotherapy or isolation of seek animals). By studying the associated farmer losses, such a modelling approach can help in increasing the economic efficiency of control measures.

6. Acknowledgments

This work was carried out with the financial support of the « ANR- Agence Nationale de la Recherche - The French National Research Agency » under the « Programme Agriculture et Développement Durable », project « ANR-05-PADD-014, ACDUQ ». 
7. References


Lesnoff, M., Thiaucourt, F., Bonnet, P., Bicout, D., Balenghien, T., Abdicho, S., Laval, G., Lancelot, R., 2002b. Un modèle conceptuel pour simuler la diffusion intra-


OIE (World Organisation for Animal Health), 2003. Handistatus II.

http://www.oie.int/hs2/.


Table 1

Parameters of the metapopulation model for the spread of contagious bovine pleuropneumonia (CBPP) in case of low virulence pathogen (LVIR)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_E$</td>
<td>Duration (in weeks) of the incubation period (state $E$)</td>
<td>6</td>
</tr>
<tr>
<td>$d_I$</td>
<td>Duration (in weeks) of the infectious period (state $I$)</td>
<td>4</td>
</tr>
<tr>
<td>$d_Q$</td>
<td>Duration (in weeks) of the chronic period (state $Q$)</td>
<td>52</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Disease-related mortality rate</td>
<td>0.036</td>
</tr>
<tr>
<td>$\beta_I$</td>
<td>Transmission rate by infectious individuals</td>
<td>0.06</td>
</tr>
<tr>
<td>$\beta_Q$</td>
<td>Transmission rate by chronic carriers</td>
<td>0</td>
</tr>
<tr>
<td>$p_{res}$</td>
<td>Proportion of naturally resistant individuals</td>
<td>0.10</td>
</tr>
<tr>
<td>$Q$</td>
<td>Proportion of individuals becoming infectious after the incubation period (from state $E$ to state $I$)</td>
<td>0.39</td>
</tr>
<tr>
<td>$b$</td>
<td>Recruitment rate</td>
<td>0.0028</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Natural mortality rate</td>
<td>0.0012</td>
</tr>
<tr>
<td>$\pi$</td>
<td>Movement rate from each herd</td>
<td>0.0033</td>
</tr>
<tr>
<td>$p_{in}$</td>
<td>Proportion of the movements occurring within the modelled zone, i.e. between two modelled herds</td>
<td>0.40</td>
</tr>
<tr>
<td>$N_x$</td>
<td>Size of herd $x$</td>
<td>1-40 (mean 8)</td>
</tr>
<tr>
<td>$T$</td>
<td>Number of interacting herds</td>
<td>100</td>
</tr>
<tr>
<td>$n$</td>
<td>Number of herds in which one herd can send animals (i.e. network degree)</td>
<td>10</td>
</tr>
</tbody>
</table>

$^a$ Parameters of the within-herd dynamics are adjusted to provide the same results as in Lesnoff et al. (2005; Tab. 1). On average in LVIR, the total number of newly infected animals (state $E$) from the disease introduction to the disease extinction represents 35% of the herd, 39% of which become infectious (state $I$), and 14% of the infectious animals die from CBPP. Values of $\mu$ and $\pi$ correspond to an annual mortality of 5% and an annual movement rate from each herd of 15%.
Table 2

Definition of the stochastic model for the within-herd spread of CBPP in herd $x$

<table>
<thead>
<tr>
<th>Event</th>
<th>Health-state transition</th>
<th>Probability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>$S_x \rightarrow E_x^1$</td>
<td>$\text{Bin}(S_x, 1 - \exp \left[ -\beta_s \sum_{k=1}^{I_x^k} \right])$</td>
</tr>
<tr>
<td>End of the latent phase</td>
<td>$E_x \rightarrow I_x^1, Q_x^1$</td>
<td>$\text{Mul}(E_x^d, q)$</td>
</tr>
<tr>
<td>End of the infectious phase</td>
<td>$I_x^d \rightarrow Q_x^1$</td>
<td>1</td>
</tr>
<tr>
<td>End of the chronic phase</td>
<td>$Q_x^d \rightarrow R_x$</td>
<td>1</td>
</tr>
<tr>
<td>Disease-related mortality</td>
<td>$I_x^k \rightarrow \text{out}$</td>
<td>$\text{Bin}(I_x^k, \alpha)$</td>
</tr>
<tr>
<td>Birth</td>
<td>$\text{in} \rightarrow S_x, R_x$</td>
<td>$\text{Mul}(\text{Bin}(N_x, b), p_{\text{res}})$</td>
</tr>
<tr>
<td>Natural mortality and movement from the herd</td>
<td>$Z_x \rightarrow \text{out}$</td>
<td>$\text{Bin}(Z_x, \mu + \pi)$</td>
</tr>
</tbody>
</table>

* $\text{Bin}$ denotes for binomial distribution, $\text{Mul}$ for multinomial distribution.
Table 3

Range of values for parameters of the metapopulation model for the spread of contagious bovine pleuropneumonia (CBPP) used to defined the scenarios and the factorial experiment in the sensitivity analysis (in bold, values of the reference scenario used in Tab. 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Range of values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha, \beta]$</td>
<td>Pathogen virulence defined by two parameters: [disease-related mortality, transmission rate by infectious animals]</td>
<td>LVIR: [0.036, 0.06], HVIR: [0.300, 0.50]</td>
</tr>
<tr>
<td>$d_Q$</td>
<td>Chronic period duration (in weeks)</td>
<td>26, 52</td>
</tr>
<tr>
<td>$\beta_Q$</td>
<td>Transmission rate by chronic carriers</td>
<td>$0, \beta_I /1000, \beta_I /100, \beta_I /50$</td>
</tr>
<tr>
<td>$b$</td>
<td>Recruitment rate</td>
<td>0.0014, 0.0028, 0.0056</td>
</tr>
<tr>
<td>$p_{in}$</td>
<td>Between-herd movement rate</td>
<td>0.0013, 0.0026</td>
</tr>
<tr>
<td>$n$</td>
<td>Network degree</td>
<td>2, 10, 99</td>
</tr>
</tbody>
</table>

$^a$LVIR: low virulence scenario; HVIR: high virulence scenario. On average in LVIR, the total number of newly infected animals (state $E$) from the disease introduction to the disease extinction represents 35% of the herd, 39% of which become infectious (state $I$), and 14% of the infectious animals die from CBPP. In HVIR, the correspondent proportions are 80, 39 and 70%.
Table 4: Definition of the outputs of the metapopulation model for the spread of contagious bovine pleuropneumonia (CBPP)

<table>
<thead>
<tr>
<th>Output</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>Individual-level reproductive number</td>
</tr>
<tr>
<td>$R^*$</td>
<td>Group-level reproductive number</td>
</tr>
<tr>
<td>$P(R_0 &gt; 1)$</td>
<td>Probability to have $R_0$ above one</td>
</tr>
<tr>
<td>$P(R^* &gt; 1)$</td>
<td>Probability to have $R^*$ above one</td>
</tr>
<tr>
<td>$\text{InfDur}$</td>
<td>Duration of the metapopulation infection</td>
</tr>
<tr>
<td>$P(\text{endemic})$</td>
<td>Probability of CBPP endemicity ($\text{InfDur} &gt; 5$ years)</td>
</tr>
<tr>
<td>$\text{EpSiz}(H)$</td>
<td>Epidemic size in infected herds (cumulative incidence in infected herds over the simulation period)</td>
</tr>
<tr>
<td>$\text{EpSiz}(I)$</td>
<td>Epidemics size in infected individuals (cumulative incidence in animals in state $E$ over the simulation period)</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1: Schematic representation of the transitions between the infections-states in herd \(x\) (\(S\): susceptible, \(E\): incubating, \(I\): infectious, \(Q\): chronic, \(R\): recovered or naturally resistant). Durations in states \(E\), \(I\) and \(Q\) are consistent (see Tab. 1 for parameters values and definition), \(Z^i_x\) being the number of animals in the \(i\)th week of state \(Z\) (\(E\), \(I\) or \(Q\)) in herd \(x\). The probability of infection for each susceptible animal in herd \(x\) is

\[
g_x = \left(1 - \exp\left(-\beta \sum_{i=1}^{\text{int}_x} I^i_x\right)\right).
\]

In each state \(Z\) in herd \(x\), the intake is \(\mathcal{O}(Z_x)\).

Figure 2: Global contributions (principal effect plus interactions) of the level of animal movement, of the network degree, of calves recruitment, of shedding period and infectiousness of chronic carriers, and of pathogen virulence to variations in model outputs. See Tab. 4 for outputs’ definitions.

Figure 3: Proportion of realisations with a simulated individual-level reproductive number above one \(P(R_0>1)\), according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers (\(\beta_Q\)) and the chronic period duration (\(d_Q\)). See Tab. 3 for parameters values associated with the scenarios, other parameters being at the reference values.

Figure 4: Proportion of realisations with a simulated group-level reproductive number above one \(P(R^*>1)\) according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers (\(\beta_Q\)), the chronic period duration (\(d_Q\)), and the movement rate. See Tab. 3 for parameters values associated with the scenarios, other parameters being at the reference values.

Figure 5: Average duration (in weeks) of the metapopulation infection (\(\text{InfDur}\)) and the associated standard error, according to the pathogen virulence (LVIR: low virulence; HVIR: high virulence).
HVIR: high virulence), the infectiousness of chronic carriers ($\beta_Q$), the chronic period
duration ($d_Q$), and the recruitment rate in each herd. See Tab. 3 for parameters values
associated with the scenarios, other parameters being at the reference values.

**Figure 6:** Probability of CBPP endemicity ($P(\text{endemic})$) defined as the proportion of
realisations with an infection duration over five years) in a bovine metapopulation of
sedentary small-sized herds, for a chronic period $d_Q = 52$ weeks, according to the
pathogen virulence (LVIR: low virulence; HVIR: high virulence), the infectiousness of
chronic carriers ($\beta_Q$), and the recruitment rate in each herd. For a chronic period of
$d_Q = 26$ weeks, $P(\text{endemic})$ is nil. See Tab. 3 for parameters values associated with the
scenarios, other parameters being at the reference values.

**Figure 7:** Average epidemic size in infected herds ($EpSiz(H)$) and the associated
standard error over a 10-year simulation period, according to the pathogen virulence
(LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers
($\beta_Q$), the chronic period duration ($d_Q$), and the recruitment rate in each herd. See Tab. 3
for parameters values associated with the scenarios, other parameters being at the
reference values. Note the change of scale, the bold dotted line in (HVIR) being the
maximum in (LVIR).

**Figure 8:** Average epidemic size in infected animals ($EpSiz(I)$) and the associated
standard error over a 10-year simulation period, according to the pathogen virulence
(LVIR: low virulence; HVIR: high virulence), the infectiousness of chronic carriers
($\beta_Q$), the chronic period duration ($d_Q$), and the recruitment rate in each herd. See Tab. 3
for parameters values associated with these scenarios, other parameters being at the
reference values.
Figure 1
Figure 2
Figure 3
Figure 4

\[ \beta_Q = 0 \]
\[ \beta_Q = \beta_I / 1000 \]
\[ \beta_Q = \beta_I / 100 \]
\[ \beta_Q = \beta_I / 50 \]
Figure 5

(LVIR)

(HVIR)
Figure 6
Figure 7

low medium high low medium high recruitment rate

\[ \frac{\beta}{Q} = \frac{\beta}{1000} \]

\[ \frac{\beta}{Q} = \frac{\beta}{100} \]

\[ \frac{\beta}{Q} = \frac{\beta}{50} \]
Figure 8

\[ \beta_Q = 0 \]
\[ \beta_Q = \frac{\beta_I}{1000} \]
\[ \beta_Q = \frac{\beta_I}{100} \]
\[ \beta_Q = \frac{\beta_I}{50} \]

**dQ = 26 weeks**
- Low recruitment rate: EpSiz(I) = 1065 +/- 894
- Medium recruitment rate: EpSiz(I) = 747
- High recruitment rate: EpSiz(I) = 474

**dQ = 52 weeks**
- Low recruitment rate: EpSiz(I) = 1160 +/- 160
- Medium recruitment rate: EpSiz(I) = 746
- High recruitment rate: EpSiz(I) = 474

**LVIR**

**HVIR**