# Disease severity declines over time after a wild boar population has been affected by Classical Swine Fever – legend or actual epidemiological process?

Supplementary material

Appendix II: Accessory investigations

Martin Lange[1], Stephanie Kramer-Schadt[2], Hans-Hermann Thulke[1]

[1] Helmholtz Centre for Environmental Research Leipzig - UFZ, Dept. of Ecological Modelling, Permoserstraße 15, D-04318 Leipzig, Germany

[2] Leibniz Institute for Zoo and Wildlife Research, Alfred-Kowalke-Straße 17, D-10315 Berlin, Germany

**Contents**

## 1. Sensitivity analysis

### 1.1 Methods

Using the model described in the main document, a sensitivity analysis for the transmission parameters $P_{\text{inf}}^{(i)}$ and $P_{\text{inf}}^{(e)}$ was conducted.

#### 1.1.1 Independent variables

The primary independent variables of the sensitivity analysis were the transmission parameters $P_{\text{inf}}^{(i)}$ and $P_{\text{inf}}^{(e)}$. $P_{\text{inf}}^{(i)}$ reflects the probability that one susceptible individual is infected from one infectious group mate within one week (internal infection). $P_{\text{inf}}^{(e)}$ is the equivalent infection probability for infecting an individual in a neighbouring group (external infection).

#### 1.1.2 Simulation experiment

The sensitivity analysis was performed for the linear $M - \mu -$ relation. For the maximum shift of case mortality per generation of infection, the maximum value of the baseline investigation in the main text $b_{virus} = 0.05$ was assumed.

For a systematic iteration over $P_{\text{inf}}^{(i)}$ and $P_{\text{inf}}^{(e)}$ in the ranges $10^{-3}$…1.0 and $10^{-4}$…0.1, respectively, the model outcome was analysed. Sampling points were placed with logarithmically scaled intervals and are shown in Figure 1.

All simulations were performed for 20 years or until host or virus went extinct. The virus was released into the boar population in a random week of the sixth year by infecting one randomly selected boar individual. For each sampling point, 120 model runs were conducted to achieve a minimum precision of $\pm 9\%$ with 95% confidence for proportions.

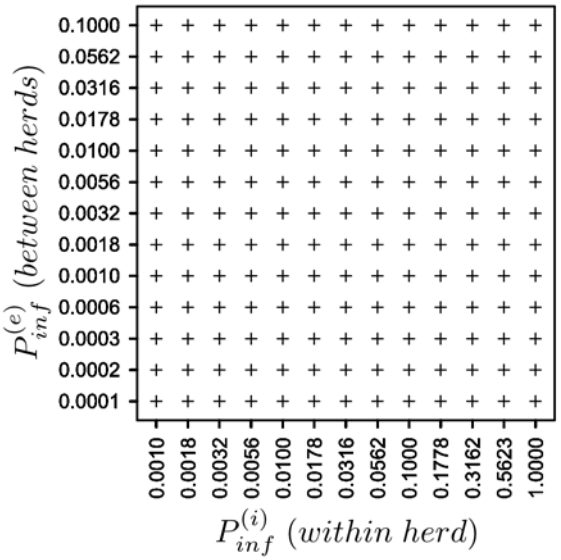


Figure 1: Sampling points of the sensitivity analysis over the transmission parameters $P_{\text{inf}}^{(i)}$ and $P_{\text{inf}}^{(e)}$

### 1.1.3 Dependent variables

The average realisation of the case mortality over the entire population of hosts was measured for each model step. Spread of the virus was recorded for each step by measuring the maximum distance of infected hosts from the release point of the virus. Moreover, the time point of each virus extinction event was recorded.

### 1.1.4 Analysis

For each parameter set, the probability of virus presence 10 years after release was calculated. The maximum achieved distance from the release point was averaged over the 120 runs per sampling point. The average case mortality was calculated over the years 10 – 15 after virus release and over all runs. Results were visualised using contour plots over the two transmission parameters.

For the sampling intervals of $P_{\text{inf}}^{(i)}$ and $P_{\text{inf}}^{(e)}$, total probabilities $P_I$ that one infectious host infects at least one further host within one week were calculated. For $P_{\text{inf}}^{(i)}$, the probability to infect at least one host in the own group $P_I^{(i)}$ was calculated, assuming a number of susceptible hosts in the group $N^{(i)}$ of 20. For $P_{\text{inf}}^{(e)}$, the probability to infect at

least one host in one of the eight neighbouring groups $P_I^{(e)}$ was calculated for a number of susceptible hosts of $N^{(e)} = 8 \cdot N^{(i)} = 160$. The total probability was calculated via

$$P_I = 1 - (1 - P_{\text{inf}})^N \tag{1}$$

where $P_{\text{inf}}$ is either $P_{\text{inf}}^{(i)}$ or $P_{\text{inf}}^{(e)}$ and $N$ is either $N^{(i)}$ or $N^{(e)}$.

## 1.2 Results

Figure 2 a) shows the average of the distance [km] the disease spreads from the release point of the virus. Establishment of the disease and successful spread through the landscape depended on sufficiently high between-group transmission potential $P_{\text{inf}}^{(e)}$. A high within-group transmission potential $P_{\text{inf}}^{(i)}$ reduces the necessary $P_{\text{inf}}^{(e)}$ by about one order of magnitude.

The probability of virus persistence over 10 years, measuring the probability to become endemic, is shown in Figure 2 b). High probability of endemicity is possible with high between-group transmission potential $P_{\text{inf}}^{(e)}$ only, while within-group transmission is of minor influence.

The outcome of pathogen evolution is measured via the average case mortality in years 10 – 15 after virus release (Figure 3 a). When the within-group transmission potential $P_{\text{inf}}^{(i)}$ is low to intermediate and the between-group transmission is intermediate, pathogen evolution results in intermediate virulence, i.e. $M \approx 0.5$. With higher within and between-group transmission, pathogen evolution leads to low virulence, i.e. $M < 0.5$.

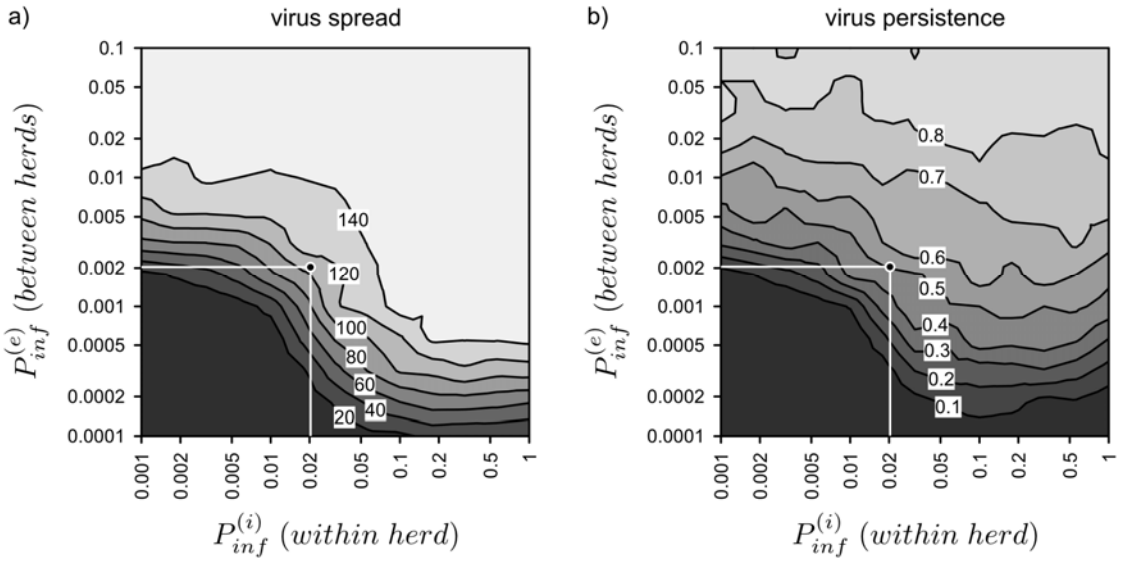


Figure 2: a) Maximum achieved distance [km] of the virus from the release point, b) probability of virus presence 10 years after release. The marker indicates the parameters of the main investigation.

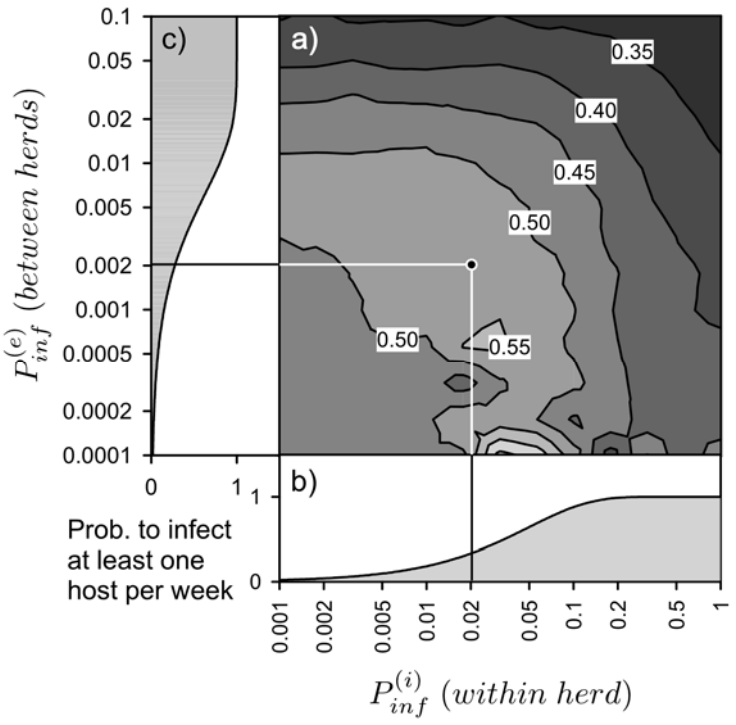


Figure 3: a) Contour plot of the mean case mortality over years 10 – 15 after virus release. Line plots along the axis show the probability that one infectious hosts

infects at least one susceptible individual within one week b) in its own group or c) in a neighbouring group. The marker indicates the parameters of the main investigation.

### 1.3 Discussion

Evolution to intermediate virulence occurs where transmission is limiting the spread of the disease, while virulence evolves to low severity where transmission is not limiting. The region of transmission parameter values that led to intermediate final virulence coincides well with the scope of intermediate disease spread (Figure 2 a). An even lower final virulence occurs for parameter sets that allow the disease to spread over the entire landscape. The latter coincides with parameter sets where one infectious host infects at least one further host within the minimum infectious period of one week as shown in Figure 3 for b) within-group and c) between-group transmission. When these probabilities reached values near 1.0, the final case mortality was below $M \approx 0.5$.

## 2. Selection on host resistance

As an alternative mechanism that could potentially alter perceived disease severity, selection on host resistance was investigated. Here, we give a brief overview of the findings of Lange et al. (2011).

### 2.1 Methods

#### 2.1.1 Host selection

Each individual host inherits its case mortality value $M_{offspring}$ from the mother ($M_{sow}$). At the beginning of a simulation run, individuals' case mortality $M$ is drawn individually from an inverse beta distribution $1–Beta(\alpha, \beta)$, i.e. the probability of transient infection is distributed as $Beta(\alpha, \beta)$. Parameters $\alpha$ and $\beta$ were selected to achieve a mean individual case mortality of $M = 0.8$ (see section 'Simulation experiments'). Pathogen evolution was discarded.

### 2.1.2 Independent variables

The primary independent variables of the study are the $M - \mu$ – relation and the initial distribution of the expected case mortality (i.e. parameters $\alpha$ and $\beta$ of the beta distribution) for host selection.

### 2.1.3 Simulation experiments

Two alternative beta distributions were used for initialisation of individual host's case mortality values: $1 - Beta(0.5, 2)$ (solid in Figure 4) and $1 - Beta(2, 8)$ (dashed in Figure 4). For both scenarios, however, average case mortality over the entire initial population was kept as 0.76.

All simulations were performed for 40 years or until host or virus went extinct. The virus was released into the boar population in a random week of the sixth year by infecting one randomly selected boar individual.

For each scenario, 500 model runs were conducted to achieve minimum precision of $\pm 5\%$ with $95\%$ confidence for proportions.

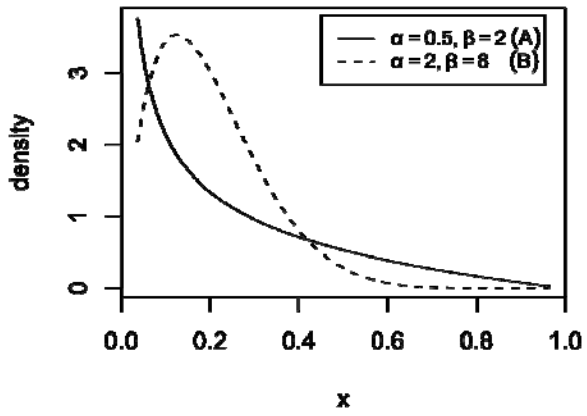


Figure 4: Probability density functions of the beta distribution as used for initialisation of individual's case mortality parameter in the host selection scenario.

### 2.1.4 Dependent variables

The average case mortality over the entire population of hosts was calculated for each time step, dividing the number of new lethal infections by the number of new lethal and transient infections.

### 2.1.5 Analysis

Case mortality measures were aggregated over 500 repetitions over the 52 weeks of each year.

## 2.2 Results

Under the host selection scenario, a 3 to 4 years phase of unchanged aggregated case mortality $\overline{M}$ with decreasing variation between runs was followed by continued decrease of aggregated case mortality values ($\overline{M}$) (see Figure 5) independent of the applied $M - \mu$ – relation. The temporal dynamics of $\overline{M}$ were strongly influenced by the distribution of $M$ in the initial population (see Figure 4):

When initial case mortalities were drawn from the beta distribution *Beta*(2, 8), the fraction of "resistant hosts", i.e. hosts a with low case mortality value, was very small which resulted in a very slow decrease of $\overline{M}$ (dashed in Figure 5). When initial values of $M$ were drawn from the beta distribution *Beta*(0.5, 2), the larger fraction of hosts with a low value of $M$ allowed for faster decline of $\overline{M}$ (solid in Figure 5).

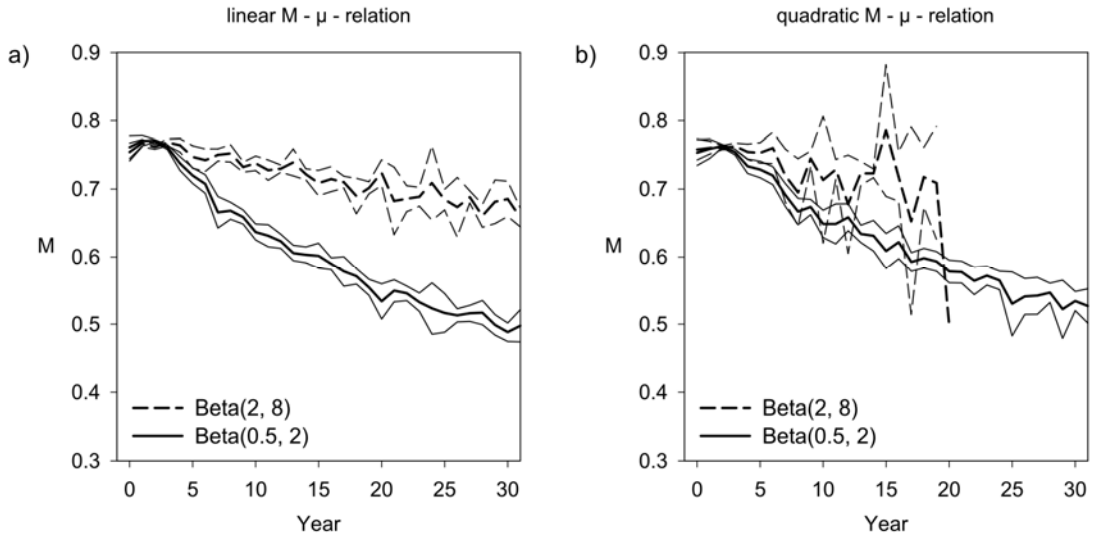


Figure 5: Mean (thick) and 95 % confidence intervals (thin) of aggregated case mortality $\overline{M}$ for host selection with a) linear, b) quadratic M – μ – relation.

## 2.3 Discussion

Assuming appropriate parameters, host selection and pathogen evolution show an efficient decline in virulence over the period of a particular outbreak. Selection on host resistance occurs much slower than pathogen evolution due to longer "generation times". The generation time of the pathogen, which is decisive for evolution, equals the time span from infection of the host until infection caused by this particular host. The mean generation time is thus even shorter than the mean infectious period $T_{inf.}$ For host selection, the evolutionary decisive generation time equals the generation time of the host, i.e. at least 6 months.

Pathogen evolution caused a rapid virulence decrease already in the epidemic phase ($1^{st}$ – $4^{th}$ year). Host evolution, on the other hand, caused a slower virulence shift which starts with the endemic phase (Figure 5). During the epidemic phase only parts of the population were affected, i.e. those where no selection had yet taken place.

Host selection was driven by the survival probability of infected hosts. Hosts that are more resistant had a higher probability to survive infection, thus had a greater reproductive success. The rate of virulence shift over time was determined by the

distribution of potential case mortalities in the initial host population. A higher fraction of hosts with a low potential case mortality, i.e. the more “resistant” hosts, results in a faster shift in virulence. Host resistance selection favours hosts with a low probability of virus-induced death. It thus works towards continuously lowering case mortality.

## 3. References

Lange, M., Kramer-Schadt, S., Thulke, H.-H., 2011. Does Severity of Classical Swine Fever Virus infection decline with time a wild boar population is infected? In: Fourichon, C., Pfeiffer, D.U. (Eds.): Proceedings SVEPM Leipzig 2011, 154-167.