Within- and between-pen transmission of Classical Swine Fever Virus: a new method to estimate the basic reproduction ratio from transmission experiments

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SUMMARY

We present a method to estimate basic reproduction ratio $R_0$ from transmission experiments. By using previously published data of experiments with Classical Swine Fever Virus more extensively, we obtained smaller confidence intervals than the martingale method used in the original papers. Moreover, our method allows simultaneous estimation of a reproduction ratio within pens $R_{0w}$ and a modified reproduction ratio between pens $R_{0b}$. Resulting estimates of $R_{0w}$ and $R_{0b}$ for weaner pigs were 100 (95% CI 54–4–186) and 7–77 (4–68–12–9), respectively. For slaughter pigs they were 15–5 (6–20–38–7) and 3–39 (1–54–7–45), respectively. We believe, because of the smaller confidence intervals we were able to obtain, that the method presented here is better suited for use in future experiments.

INTRODUCTION

Classical Swine Fever (CSF) or hog cholera is a highly contagious pig disease [1–3], an epidemic of which can cause huge problems like reduction in animal welfare, and high economic losses as a result of export limitations and mass destruction [4]. The disease is caused by the Classical Swine Fever Virus (CSFV) [1–3]. Transmission of the virus between pigs can be quantified by estimating parameters from transmission experiments, in which a number of pigs within a pen are inoculated with the virus and the transmission process in followed [5]. An important parameter of virus transmission is the basic reproduction ratio $R_0$, defined as the number of secondary infected individuals caused by one typical infectious individual in an infinite susceptible population. If $R_0$ is smaller than 1, then on average every infectious animal infects less than one other animal causing the outbreak to wane. If on the other hand $R_0$ is greater than 1, major outbreaks can occur [6].

In 1998 and 1999 Laevens et al. did two transmission experiments with CSFV; one with weaner pigs and the other with slaughter pigs [7, 8]. In both experiments there were 3 adjacent pens with either 15 weaner pigs or 6 slaughter pigs in each pen. In the middle pen one pig was inoculated with CSFV and every 2 days blood samples of all the pigs were taken to measure viraemia. From these measurements the infectious period of every pig was reconstructed by assuming that a pig is infectious when it is viraemic. Subsequently $R_0$ was estimated using the martingale estimation method, based on the stochastic SIR model [5, 9]. This model describes transmission of a virus in a group of animals by describing the change in the numbers of susceptible ($S$) and infectious ($I$) animals in terms of these numbers and the total number of animals ($N$). In the model, infection of susceptible animals and recovery of infectious animals are assumed to be generated by a Poisson process with...
Table 1. Course of transmission experiments

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Division of the virus transmission process in 2-day time periods, stratified by pen. Time starts at day of inoculation. S is the number of susceptible animals at the start of the interval; I is the number of infectious animals; C is the number of new cases and N is the total number of animals, where 0–5 is an animal present for only 1 of 2 days in a certain category.

rates $\beta SI/N$ and $\alpha I$, where $\beta$ and $\alpha$ are the transmission and recovery parameter, respectively. The $R_0$ is estimated from the number of animals ultimately infected during the experiment, when no susceptible or no infectious animals remain. The sum of the fractions of infectious periods remaining when the last susceptible animal is infected is used if relevant. Laevens et al. [7, 8] used only the data of the middle pen to estimate $R_0$ because in the other pens transmission was not solely caused by infectious animals in the same pen. The estimates obtained were 81.3 (s.e. 109, i.e. 95% CI $132–295$) and 13.7 (s.e. 13.7, i.e. 95% CI $13-2-406$) for weaner and slaughter pigs, respectively. This meant that despite the fact that the infection process took place very quickly and all animals were infected, the estimated $R_0$s were not significantly greater than 1. Since some aspects of the data were not used for the estimation (infection times and infectious periods of all animals known for all three pens), searching for an alternative estimation method would be worthwhile, using as much information from the data as possible. Hopefully this will lead to a smaller confidence interval.

In an attempt to obtain an $R_0$ estimate with a smaller confidence interval, we did separate estimations of $\beta$, the infectivity parameter, and $\alpha$, the recovery parameter, which are used to calculate $R_0$ ($R_0 = \beta/\alpha$). For $\beta$ estimation, the infection process was partitioned into intervals with known numbers of infection cases ($C$) and susceptible ($S$) and infectious ($I$) animals. These sets of $(S, I, C)$ were used to construct a likelihood function, which we maximized to get a maximum likelihood estimator for $\beta$. For $\alpha$ estimation, the lengths of the infectious periods were used to fit a generalized linear model.

**MATERIALS AND METHODS**

We used the data obtained in the transmission experiments of Laevens et al. (for more detail see [7,
In both experiments there were 3 adjacent pens with equal numbers of pigs: 15 weaner pigs in one experiment and 6 slaughter pigs in the other. One of the pigs in the middle pen was inoculated with CSFV and every 2 days blood samples were taken from all animals, which were tested for viraemia. From these data the infectious period of each pig was reconstructed, assuming that the animal is infectious when it is viraemic.

By assuming a latent period of 6 days (infected but not yet infectious) [2], we were able to reconstruct the entire virus transmission process in the three pens. These reconstructions enabled us to estimate the parameters, by using the following stochastic SIR model [6], incorporating both within- and between-pen transmission:

\[
\begin{align*}
rate(S \rightarrow S-1) &= (\beta_w I_w/N_w + \beta_b I_b/N_b) S \\
rate(I \rightarrow I-1) &= \alpha I.
\end{align*}
\]

(1) (2)

In this model, \(\beta_w\) is the within-pen transmission parameter defined as the expected number of new infections in the same pen per day per typical infectious animal in a fully susceptible population. Likewise, \(\beta_b\) is the between-pen transmission parameter defined as the expected number of new infections in other pens per day per typical infectious animal in a fully susceptible population. The parameter \(\alpha\) represents the recovery rate per infectious animal. Because there are two transmission parameters \(\beta_w\) and \(\beta_b\), we also make a distinction between a within-pen reproduction ratio \(R_{0w}\) and a between-pen reproduction ratio \(R_{0b}\). \(R_{0w}\) is defined as the expected number of new infections caused by one infectious animal in the same pen. \(R_{0b}\) is defined as the expected number of secondary infected pens caused by one infectious pen, considering a pen as infected when at least one pig is infected. Estimates for \(R_{0w}\) and \(R_{0b}\) can be calculated as follows:

\[
R_{0w} = \frac{\beta_w}{\alpha}
\]

(3)

\[
R_{0b} = R_{0b}' \cdot E(I_{tot}) = \frac{\beta_b}{\alpha} \cdot E(I_{tot}).
\]

(4)

In this equation, \(E(I_{tot})\) is the expected number of animals ultimately infected within one pen. \(E(I_{tot})\) can under our model assumptions easily be determined if \(R_{0w}\) is known [10], but will not be further discussed in this paper. \(R_{0b}'\) is the expected number of secondary infected pens caused by one infectious animal. \(R_{0b}'\), being independent of \(E(I_{tot})\), is the parameter that will be estimated in this paper. For notational convenience, we have introduced the vectors \(\vec{\beta} = (\beta_w, \beta_b)\), \(\log \hat{\vec{\beta}} = (\log \beta_w, \log \beta_b)\), \(\vec{R}_0 = (R_{0w}, R_{0b})\), and \(\log \hat{R}_0 = (\log R_{0w}, \log R_{0b})\). Because infection and recovery are independent processes, \(\hat{R}_0\) was calculated from separate estimations of \(\vec{\beta}\) and \(\alpha\).

In order to estimate transmission parameters \(\vec{\beta}\), the infection process has been divided into time intervals of two days, the intervals between two subsequent samplings. For each interval, the number of susceptible pigs at the start of the interval (\(S\)), the number of infectious pigs (\(I\)) and the number of new cases (\(C\)) was determined (Table 1). In each time interval \(k\), the probability of a susceptible animal escaping infection from the constant rate \((\beta_w I_w/N_w + \beta_b I_b/N_b)\) is, according to the Poisson distribution, \(e^{-(\beta_w I_w/N_w + \beta_b I_b/N_b) t_k}\). Therefore, the probability of getting \(C_k\) cases, with \(S_k\) susceptibles and \(i_k\) infected animals in the same pen and \(j_k\) infected animals in the other pens is, according to the binomial distribution:

\[
\text{prob}(C_k | i_k, j_k, S_k) = \binom{S_k}{C_k} (1 - e^{-\beta_w i_k t_k})^C_k (e^{-\beta_w i_k t_k} + \beta_b j_k/N_b)^C_k. 
\]

(5)

The probabilities for all time intervals have been used to make up the log-likelihood function, which may be written as:

\[
\log L(\beta_w, \beta_b) = \sum_k [C_k \log (e^{\beta_w i_k + \beta_b j_k}/S_k) - S_k (\beta_w i_k + \beta_b j_k)].
\]

(6)

where \(\log (S_k)\) has been omitted because it plays no role. Maximising this function results in maximum likelihood estimators for \(\beta_w\) and \(\beta_b\).

Three methods were used to derive confidence intervals for \(\beta_w\). After comparing several features (e.g. mathematical background, practical value), a decision was made as to which method should be used for interval estimation of \(\beta_w\), \(R_{0w}\) and \(R_{0b}\). The first method, which we shall refer to as the construction method, is based on the likelihood ratio and on the equivalence of testing and construction of a confidence interval. The test used here is derived from the observation that the likelihood ratio for testing one value of \(\beta_w\) (\(H_0\): \(\beta_w = \beta_0\)) against another value of \(\beta_w\) (\(H_1\): \(\beta_w = \beta' < \beta_0\)) is a monotonic and decreasing function of each \(C\). It allowed us to construct a critical
The recovery/death rate parameter $\alpha$ has been estimated using a generalized linear model for survival analysis with censoring, as described by Aitken et al. [13]. In this model for each animal two explanatory variables $T_k$ and $y_k$ can be observed. The first one, $T_k$, is the observed length of the infectious period. The second one, $y_k$, is a censoring variable: $y_k = 1$ if $T_k$ is the true survival time, whereas $y_k = 0$ if the true survival time is greater than $T_k$. The likelihood function reads as follows:

$$L(\alpha) = \prod_{k=1}^{n} (ze^{-\alpha T_k})^{y_k} (e^{-\alpha T_k})^{1-y_k} = \prod_{k=1}^{n} z^{y_k} e^{-\alpha T_k}$$

$$= \prod_{k=1}^{n} (\alpha T_k)^{y_k} e^{-\alpha T_k} / \prod_{k=1}^{n} T_k^{y_k} \cdot \alpha. \quad (8)$$

The second method is the likelihood ratio ($\lambda$) test as described by Neyman and Pearson (reference in [11]), which relies on the asymptotic chi-square distribution of $-2\log \lambda$ with, in our case, 1 degree of freedom. Unfortunately, the computation is almost prohibitively time-consuming, and just how to construct a confidence area for the parameter vector $\beta$ or how to determine confidence intervals for $R_0$ is not clear. The first method is the likelihood ratio ($\lambda$) test as described by Neyman and Pearson (reference in [11]), which relies on the asymptotic chi-square distribution of $-2\log \lambda$ with, in our case, 1 degree of freedom. This method calculates 95% confidence limits by solving the equation $-2\log \lambda = 3.84$ for one of the two $\beta$s ($\beta_w$ or $\beta_s$) treating the other as a constant as its estimate. This is a much faster method than the first one; nonetheless it suffers from the same construction difficulties with regard to simultaneous confidence intervals. The third method is based on the asymptotic (multivariate) normal distribution of a maximum likelihood estimator [12]. The assumption is made that the estimator of $\log \beta$ (instead of $\hat{\beta}$), being also a ML-estimator, is asymptotically normally distributed because then non-realistic (negative) values of $\beta_w$ and $\beta_s$ cannot occur. This results in the following covariance matrix $M$:

$$M = \begin{pmatrix}
\frac{\partial^2 \log L}{\partial (\log \beta_w)^2} & \frac{\partial^2 \log L}{\partial (\log \beta_w)(\log \beta_s)} \\
\frac{\partial^2 \log L}{\partial (\log \beta_s)(\log \beta_w)} & \frac{\partial^2 \log L}{\partial (\log \beta_s)^2}
\end{pmatrix}^{-1}. \quad (7)$$

This method is computationally fast and, since it provides an estimate of the covariance matrix, it obviously enables construction of confidence areas for $\log \beta$ and $\log R_0$.†

† Note that, if only one transmission parameter is estimated, this likelihood variance method is in fact the same as a generalized linear model with response variate $C$, binomially distributed with index $S$, and a complementary log-log LINK function, and $\log(I/N)$ as offset. Because in this case we want to estimate two transmission parameters simultaneously, it is not possible to use this GLM.
intervals of (4.98–14.6) and (0.817–4.18). Because the construction method does not assume specific distributions based on asymptotic features, we believe that the estimated confidence intervals from this method would be the most precise. The log λ method, which is much faster than the numerical method, performed quite well, while the likelihood variance method resulted in slightly upwards shifted intervals. However, we decided to use this last-mentioned method for further calculations, because the obtained covariance matrices for λ together with the variances for z can be used to estimate covariance matrices for \( \tilde{R}_n \).

The covariance matrices \( M \) of \( \log \beta \) thus calculated were:

\[
M_{\text{weaner}} = \begin{pmatrix}
0.0752 & -0.00128 \\
-0.00128 & 0.0438
\end{pmatrix}
\]  \( (11) \)

\[
M_{\text{slaughter}} = \begin{pmatrix}
0.175 & -0.0132 \\
-0.0132 & 0.118
\end{pmatrix}
\]  \( (12) \)

To compare the estimated \( \log \beta \)s of weaner and slaughter pigs, the difference of the two was calculated (\( \Delta \log \beta \)), together with the accompanying covariance matrix, \( M_{\text{weaner}} + M_{\text{slaughter}} \). The 95% confidence area of this difference in Figure 1 shows that this area does not cross the line \( \Delta \log \beta_w = 0 \) and therefore the \( \log \beta \)s of weaner and slaughter pigs differ significantly. This is not the case for the \( \log \beta \)s. Estimation of recovery parameter \( \alpha \) resulted in a \( \log \alpha \) for weaner pigs of \(-2.47 \pm 0.0231\) and for slaughter pigs of \(-2.13 \pm 0.0433\).

Estimation of \( \log \tilde{R}_n \) resulted in these vectors and covariance matrices:

\[
\log \tilde{R}_{0,\text{weaner}} = \begin{pmatrix}
4.61 \\
2.05
\end{pmatrix}
\]

and covariance matrix

\[
\begin{pmatrix}
0.0983 & 0.0218 \\
0.0218 & 0.0669
\end{pmatrix}
\]  \( (13) \)

\[
\log \tilde{R}_{0,\text{slaughter}} = \begin{pmatrix}
2.74 \\
1.22
\end{pmatrix}
\]  \( \Delta \log R_{0w} \)

and covariance matrix

\[
\begin{pmatrix}
0.218 & 0.0300 \\
0.0300 & 0.162
\end{pmatrix}
\]  \( \Delta \log R_{0s} \)

This means that the estimated \( R_{0w} \) and \( R_{0s} \) for weaner pigs were 100 (CI 54.4–186) and 7.77 (CI 4.68–12.9), and for slaughter pigs 15.5 (CI 6.20–38.7) and 3.39 (CI 1.54–7.45), respectively. Testing whether \( \log \tilde{R}_{0,\text{weaner}} \) differs from \( \log \tilde{R}_{0,\text{slaughter}} \) has been done by calculating the difference and accompanying covariance matrix, and subsequently plotting the 95% confidence area (Fig. 2). It illustrates that the confidence area does not cross the line \( \Delta \log R_{0w} = 0 \), but does cross the line \( \Delta \log R_{0s} = 0 \). Therefore, the conclusion is that \( R_{0w} \) differs between weaner and slaughter pigs, but \( R_{0s} \) does not.

**DISCUSSION**

The maximum likelihood method presented in this paper resulted in a much smaller confidence interval of \( R_{0w} \) than the martingale method [7, 8]. This was probably due to the more extensive use of the data, by dividing the virus transmission process into intervals with known numbers of new cases and susceptible and infectious pigs. Also, the maximum likelihood method uses data from all the pens, in contrast with the martingale method, which only uses the data of the middle (the primarily infected) pen. We are convinced that the method presented here is more suitable to be used in data analysis of future experiments.

Three different methods were used to calculate confidence intervals for \( \beta_w \): a construction method based on the likelihood ratio \( \lambda \), the \( \log \lambda \) method, and the likelihood variance method. The construction method is not based on asymptotic features (i.e. many data points), and is in this sense a reliable method. However, its disadvantages were that the calculation time was long, it was impossible to construct a confidence area for two parameters (\( \beta_w \) and \( \beta_s \)) simultaneously, and it was not possible to use the results to construct intervals for \( R_n \). The other two methods are based on asymptotic features of the \( -2 \log \lambda \) and of the likelihood function itself. Both of these methods are fast. The advantage of the \( \log \lambda \) method is that it uses the likelihood ratio, just like the construction method, and that the results are very similar. The advantage of the likelihood variance method, however, is that it allows derivation of
mainly due to more intensive animal contacts, this is with other CSF strains as well. If the difference is units with older pigs (in a finishing herd). Therefore it (weaner pigs in a sow herd) will be quicker than in

A more surprising result was the significant difference between the two age groups: the \( R_{ow} \) of weaner pigs is larger than the \( R_{ow} \) of slaughter pigs. This can be due to several causes, which should be judged by the fact that the \( R_{ow}'s \) do not differ. First, the resistance to infection in younger pigs could be lower (higher susceptibility). Second, the smaller volume of resistance to infection in younger pigs might have more intensive contacts with each other, which is the most probable cause, because the first two mentioned would also result in higher \( R_{ow}'s \). However, it is also possible that the \( R_{ow}'s \) do differ, but that this was not observed in these experiments.

From an epidemiological point of view, the difference between the groups can be important because virus transmission in units with younger pigs

\[
\begin{align*}
\log \lambda &= \log \left[ \prod_{j=1}^{m} \prod_{k=1}^{n_j} \left( S_j - \sum_{l=0}^{k-1} C_{jl} \right) \frac{1}{e^{\beta_j} \sigma_j} \right] \\
&= \sum_{j=1}^{m} \sum_{k=1}^{n_j} \left[ C_{jk} \left( \log \frac{1}{1 - e^{-\beta_j}} \right) + S_j - \sum_{l=1}^{k} C_{jl} \right] (\beta_j - \beta_0)
\end{align*}
\]

(weaner pigs in a sow herd) will be quicker than in units with older pigs (in a finishing herd). Therefore it is important to know whether this difference exists with other CSF strains as well. If the difference is mainly due to more intensive animal contacts, this is to be expected.

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**APPENDIX**

Here a numerical method is derived to construct confidence intervals (CI) for the transmission parameters \( \beta \). To keep the derivation more orderly, it is shown here for only one transmission parameter \( \beta \), as if there were only within-pen transmission. When the other parameter is kept constant, as in the examples in the text, the derivation is similar. The log-likelihood equation with one parameter \( \beta \) is, analogous to (6):

\[
\log L(\beta) = \sum_{k} [C_k \log(e^{\beta_k} - 1) - S_k(\beta_k)].
\]

Now, with the equivalence of testing and CI construction in mind, a test is suggested of \( H_0: \beta = \beta_0 \), against \( H_1: \beta = \beta' < \beta_0 \). Then, letting \( \beta' \) tend to \( \beta_0 \), a test will be obtained to test \( \beta_0 \) against any \( \beta' < \beta_0 \). This test can be used to construct an upper limit of a confidence interval. A similar procedure is followed for the lower limit.

The test, \( \Phi \), is based on the likelihood ratio (\( \lambda \)) [15]:

\[
\Phi = \begin{cases} 
1 & \text{if } \log \lambda \geq d \\
0 & \text{if } \log \lambda < d
\end{cases}
\]

where \( d \) is determined by \( E_{p_h}(\Phi) = 0.05 \) (for a 95% CI). \( H_0 \) is rejected when \( \Phi = 1 \) and \( H_0 \) is not rejected when \( \Phi = 0 \). In (16), \( \log \lambda \) is:

\[
\frac{\partial \log \lambda}{\partial C_{jk}} = a_{jk} + \sum_{l=1}^{n_j} b_{jl} \leq 0
\]

where \( a_{jk} = \log \frac{1-e^{-\beta_j}}{1-e^{-\beta_{0j}}} \) and \( b_{jl} = i_{jk}(\beta' - \beta_0) \).

Observe that \( \log \lambda \) is monotonically decreasing in every \( C_{jk} \):

\[
\Rightarrow \beta \sum_{l=1}^{n_j} i_{jl} + \log[1-e^{\beta'j}] \leq \beta_0 \sum_{l=1}^{n_j} i_{jl} + \log[1-e^{\beta_0j}],
\]
which is true since \( g_{jk}(\beta) = \beta \sum_{i=1}^{n_j} i_{jk} + \log[1 - e^{-\beta i_{jk}}] \) is a monotonic and increasing function of \( \beta \).

Hence, \( \log \lambda \) can be used to construct a test for \( \beta' < \beta_0 \).

The test is constructed for any \( \beta' < \beta_0 \) (upper limit) by letting \( \beta' \) tend to \( \beta_0 \) (\( \beta' \rightarrow \beta_0 \)), which results in:

\[
a_{jk} + \sum_{i=1}^{n_j} b_{ij} = \left[ \log[1 - e^{-\beta i_{jk}}] + \sum_{i=1}^{n_j} i_{jk} \beta' \right] - \left[ \log[1 - e^{-\beta i_{jk}}] + \sum_{i=1}^{n_j} i_{jk} \beta_0 \right] \\
= (\text{via Taylor expansion}) \approx \left( \beta' - \beta_0 \right) r_{jk}, \tag{18}
\]

where \( r_{jk} = \left( \frac{i_{jk}}{e^{\beta i_{jk}} - 1} + \sum_{i=1}^{n_j} i_{jk} \right) \). Hence, \( \log \lambda \) becomes:

\[
\log \lambda = \sum_{j=1}^{m} \sum_{k=1}^{n_j} \left[ C_{jk}(\beta' - \beta_0) r_{jk} \right] - S_{jk}(\beta' - \beta_0), \tag{19}
\]

which determines the form of the test for the upper limit (since all other factors are independent of \( \beta_0 \)):

\[
\Psi = \begin{cases} 
1 \quad \text{if } \sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} \leq d \\
0 \quad \text{if } \sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} > d
\end{cases} \tag{20}
\]

For the case \( \beta' > \beta_0 \) (lower limit), the derivation is the same, except for the inequality signs in formula (20), which are switched.

The test is used for an iterative search of that \( \beta_0 \) for which holds:

\[
E(\Psi) = 0.025, \quad \text{and} \quad \sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} = d.
\]

REFERENCES