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

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Table 1. *Course of transmission experiments*

Time (days):		4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20	20–22	22–24
Weaner pigs											
pen 1	S	15	15	15	15	13	7	4	2		
	I	0	0	0	0	0	0	1	5		
	C	0	0	0	2	6	3	2	2		
	N	15	15	15	15	15	15	15	15		
pen 2	S	14	5	0	0	0	0	0	0		
	I	1	1	1	5·5	12	11·5	10	10		
	C	9	5	0	0	0	0	0	0		
	N	15	15	15	15	14·5	11·5	10	10		
pen 3	S	13	13	13	13	6	3	1	0		
	I	0	0	0	0	0	0	3·5	8·5		
	C	0	0	0	7	3	2	1	0		
	N	14	14	14	14	13	13	13	13		
Slaughter pigs											
pen 1	S	5	5	5	5	5	4	4	3	1	1
	I	0	0	0	0	0	0	0	0·5	1	1·5
	C	0	0	0	0	1	0	1	2	0	1
	N	6	6	6	6	6	6	6	6	5	5
pen 2	S	5	4	3	1	0	0	0	0	0	0
	I	0·5	1	1	1	1·5	3	4·5	5	4·5	4
	C	1	1	2	1	0	0	0	0	0	0
	N	6	6	6	6	6	6	6	6	6	6
pen 3	S	6	6	6	6	6	6	6	2	0	0
	I	0	0	0	0	0	0	0	0	0	2
	C	0	0	0	0	0	0	4	2	0	0
	N	6	6	6	6	6	6	6	6	6	6

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 αI, where β and α 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 −13·2–40·6) 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_0s 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 β, the infectivity parameter, and α, the recovery parameter, which are used to calculate R_0 ($R_0 = \beta/\alpha$). For β 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 β. For α 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,

8]). 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:

$$\text{rate}(S \to S-1) = (\beta_w I_w/N_w + \beta_b I_b/N_b)S \quad (1)$$
$$\text{rate}(I \to I-1) = \alpha I. \quad (2)$$

In this model, β_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, β_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 α represents the recovery rate per infectious animal. Because there are two transmission parameters β_w and β_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 secondary infected animals caused by one typical infectious animal in the same pen. R_{0b} is defined as the expected number of secondary infected pens caused by one typical 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:

$$R_{0w} = \frac{\beta_w}{\alpha} \quad (3)$$

$$R_{0b} = R'_{0b} \cdot E(I_{\text{tot}}) = \frac{\beta_b}{\alpha} \cdot E(I_{\text{tot}}). \quad (4)$$

In this equation, $E(I_{\text{tot}})$ is the expected number of animals ultimately infected within one pen. $E(I_{\text{tot}})$ 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 typical infectious *animal*.

R'_{0b}, being independent of $E(I_{\text{tot}})$, is the parameter that will be estimated in this paper. For notational convenience, we have introduced the vectors $\vec{\beta} = (\beta_w, \beta_b)$, $\log \vec{\beta} = (\log \beta_w, \log \beta_b)$, $\vec{R}_0 = (R_{0w}, R'_{0b})$, and $\log \vec{R}_0 = (\log R_{0w}, \log R'_{0b})$. Because infection and recovery are independent processes, $\vec{R}_0$ was calculated from separate estimations of $\vec{\beta}$ and α.

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 $(\beta_w I_{wk}/N_{wk} + \beta_b I_{bk}/N_{bk})$ is, according to the Poisson distribution, $e^{-(\beta_w I_{wk}/N_{wk} + \beta_b I_{bk}/N_{bk})}$. Therefore, the probability of getting C_k cases, with S_k susceptibles and i_k as the fraction of infectious pigs (I_k/N_k) in the same pen and j_k as the fraction of infectious pigs in the other pens is, according to the binomial distribution:

$$\text{prob}(C_k|i_k, j_k, S_k)$$
$$= \binom{S_k}{C_k}(1-e^{-\beta_w j_k - \beta_b j_k})^{C_k}(e^{-\beta_w j_k - \beta_w j_k})^{S_k - C_k}. \quad (5)$$

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

$$\log L(\beta_w, \beta_b) = \sum_k [C_k \log(e^{\beta_w j_k + \beta_b j_k} - 1)$$
$$- S_k(\beta_w i_k + \beta_b j_k)], \quad (6)$$

where $\log\binom{S_k}{C_k}$ has been omitted because it plays no role. Maximising this function results in maximum likelihood estimators for β_w and β_b.

Three methods were used to derive confidence intervals for β_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 β_b, 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 β_w (H$_0$: $\beta_w = \beta_0$) against another value of β_w (H$_A$: $\beta_w = \beta' < \beta_0$) is a monotonic and decreasing function of each C. It allowed us to construct a critical
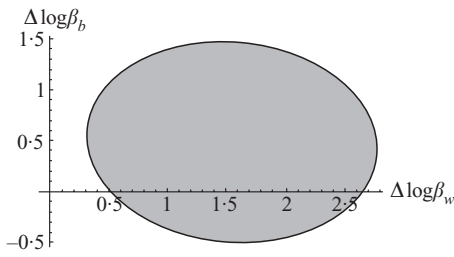
Fig. 1. Shaded area is the 95% confidence area for $\Delta\log\vec{\beta}$.

region for the C by using the probability function of C itself, without invoking any approximate probability distribution of the likelihood ratio. For details, see the appendix. With this method confidence intervals can be constructed for one of the two βs (β_w or β_b) treating the other as a constant as its estimate. Unfortunately, the computation is almost prohibitively time-consuming, and just how to construct a confidence area for the parameter *vector* $\vec{\beta}$ or how to determine confidence intervals for R_0 is not clear. The second method is the likelihood ratio (λ) 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 βs (β_w or β_b) 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 $\log\vec{\beta}$ (instead of $\vec{\beta}$), being also a ML-estimator, is asymptotically normally distributed because then non-realistic (negative) values of β_w and β_b cannot occur. This results in the following covariance matrix **M**:

$$\mathbf{M} = -\begin{bmatrix} \dfrac{\partial^2 \log L}{\partial(\log\beta_w)^2} & \dfrac{\partial^2 \log L}{\partial(\log\beta_w)(\log\beta_b)} \\ \dfrac{\partial^2 \log L}{\partial(\log\beta_w)(\log\beta_b)} & \dfrac{\partial^2 \log L}{\partial(\log\beta_b)^2} \end{bmatrix}^{-1}.\quad(7)$$

This method is computationally fast and, since it provides an estimate of the covariance matrix, it obviously enables construction of confidence areas for $\log\vec{\beta}$ and $\log\vec{R}_0$†.

† 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.

The recovery/death rate parameter α 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 is 1 if T_k is the true survival time, whereas y_k is 0 if the true survival time is greater than T_k. The likelihood function reads as follows:

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

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

The kernel of this likelihood is the same as it would be with a set of n observations y_k each having an independent Poisson distribution with mean αT_k (see [13]). The analysis was performed in Genstat [14], using the RSURVIVAL procedure, where y_k denotes the response variate, $\log T_k$ the offset, and the model is fitted with a log LINK function and a Poisson distribution. The output is an estimate of $\log\alpha$ and its estimated variance.

The estimator of $\log\vec{R}_0$ is given by:

$$\log\vec{R}_0 = \log\vec{\beta}-\log\alpha.\quad(9)$$

Derivation of a confidence area for $\log\vec{R}_0$ is done by adding the covariance matrices for $\log\vec{\beta}$ and $\log\alpha$:

$$\mathrm{var}(\log\vec{R}_0) = \mathrm{var}(\log\vec{\beta})+\mathrm{var}(\log\alpha)\begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix}.\quad(10)$$

The estimated $\log\vec{R}_0$s and $\mathrm{var}(\log\vec{R}_0)$s for weaner and slaughter pigs were used to construct a confidence area for the difference of the two $\log\vec{R}_0$s, and to assess whether R_{0w} or R'_{0b} differ significantly between weaner and slaughter pigs.

RESULTS

The maximum likelihood estimation method used to estimate transmission parameters β_w and β_b produced point estimates of 8·52 and 0·656 for weaner pigs and 1·85 and 0·402 for slaughter pigs, respectively. Three methods were used to determine 95% confidence intervals for β_w. With the construction method based on the likelihood ratio λ, the intervals for β_w obtained were (4·77–14·1) and (0·704–3·63) for weaner pigs and slaughter pigs, respectively. With the $\log\lambda$ method the intervals were (4·78–14·1) and (0·709–3·79), respectively, and the likelihood variance method produced

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 $\log \lambda$ 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 $\vec{\beta}$ together with the variances for α can be used to estimate covariance matrices for $\vec{R}_0$.

The covariance matrices $\mathbf{M}$ of $\log \vec{\beta}$ thus calculated were:

$$\mathbf{M}_{\text{weaner}} = \begin{pmatrix} 0.0752 & -0.00128 \\ -0.00128 & 0.0438 \end{pmatrix} \qquad (11)$$

$$\mathbf{M}_{\text{slaughter}} = \begin{pmatrix} 0.175 & -0.0132 \\ -0.0132 & 0.118 \end{pmatrix}. \qquad (12)$$

To compare the estimated $\log \vec{\beta}$s of weaner and slaughter pigs, the difference of the two was calculated ($\Delta \log \vec{\beta}$), together with the accompanying covariance matrix, $\mathbf{M}_{\text{weaner}} + \mathbf{M}_{\text{slaughter}}$. 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 $\log \beta_w$s of weaner and slaughter pigs differ significantly. This is not the case for the $\log \beta_b$s. Estimation of recovery parameter α resulted in a $\log \alpha$ for weaner pigs of $-2\cdot47$ with variance $0\cdot0231$ and for slaughter pigs of $-2\cdot13$ with variance $0\cdot0433$.

Estimation of $\log \vec{R}_0$ resulted in these vectors and covariance matrices:

$$\log \vec{R}_{0\,\text{weaner}} = \begin{pmatrix} 4.61 \\ 2.05 \end{pmatrix}$$

and covariance matrix

$$\begin{pmatrix} 0.0983 & 0.0218 \\ 0.0218 & 0.0669 \end{pmatrix} \qquad (13)$$

$$\log \vec{R}_{0\,\text{slaughter}} = \begin{pmatrix} 2.74 \\ 1.22 \end{pmatrix}$$

and covariance matrix

$$\begin{pmatrix} 0.218 & 0.0300 \\ 0.0300 & 0.162 \end{pmatrix}. \qquad (14)$$

This means that the estimated R_{0w} and R'_{0b} 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 $\log \vec{R}_{0\,\text{weaner}}$
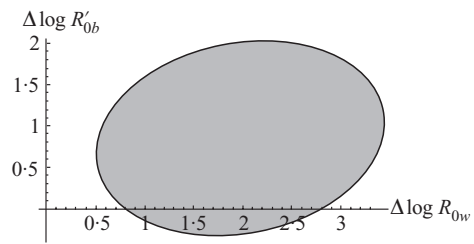

Fig. 2. Shaded area is the 95% confidence area for $\Delta \log \vec{R}_0$.

differs from $\log \vec{R}_{0\,\text{slaughter}}$ 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 $\Delta \log R'_{0b} = 0$. Therefore, the conclusion is that R_{0w} differs between weaner and slaughter pigs, but R'_{0b} 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 β_w: a construction method based on the likelihood ratio λ, 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 (β_w and β_b) simultaneously, and it was not possible to use the results to construct intervals for R_0. 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

confidence areas for β_w and β_b simultaneously and that the estimated variances can be used to obtain variances of the $\log \vec{R}_0$ estimates. That is why this likelihood variance method is used to estimate variances for β_b and $\log \vec{R}_0$ as well.

With the maximum likelihood method presented in this paper, the R_{0w} and R'_{0b} appeared to be significantly greater than 1 for both weaner and slaughter pigs. This conclusion could not be made from the martingale estimation, but was expected because of the large outbreak in both experiments (all animals infected) and the ability of the virus to cause CSF epidemics.

A more surprising result was the significant difference between the two age groups: the R_{0w} of weaner pigs is larger than the R_{0w} of slaughter pigs. This can be due to several causes, which should be judged by the fact that the R'_{0b}s do not differ. First, the resistance to infection in younger pigs could be lower (higher susceptibility). Second, the smaller volume of younger pigs could be responsible for a higher virus concentration in the animals and consequently a higher virus excretion (higher infectiousness). Third, weaner 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'_{0b}s. However, it is also possible that the R'_{0b}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

APPENDIX

Here a numerical method is derived to construct confidence intervals (CI) for the transmission parameters $\vec{\beta}$. To keep the derivation more orderly, it is shown here for only one transmission parameter β, 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 β is, analogous to (6):

$$\log L(\beta) = \sum_k [C_k \log(e^{\beta i_k} - 1) - S_k(\beta i_k)]. \tag{15}$$

Now, with the equivalence of testing and CI construction in mind, a test is suggested of $H_0: \beta = \beta_0$, against $H_A: \beta = \beta' < \beta_0$. Then, letting β' tend to β_0, a test will be obtained to test β_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, Φ, is based on the likelihood ratio (λ) [15]:

$$\Phi = \begin{cases} 1 \text{ if } \log \lambda \geqslant d \\ 0 \text{ if } \log \lambda < d \end{cases}, \tag{16}$$

where d is determined by $E_{\beta_0}(\Phi) = 0.05$ (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:

$$
\begin{aligned}
\log \lambda &= \log \left[\frac{\prod_{j=1}^{m} \prod_{k=1}^{n_j} \binom{S_j - \sum_{l=0}^{k-1} C_{jl}}{C_{jk}} (1 - e^{-\beta' i_{jk}})^{C_{jk}} (e^{-\beta' i_{jk}})^{S_j - \sum_{l=1}^{k} C_{jl}}}{\prod_{j=1}^{m} \prod_{k=1}^{nj} \binom{S_l - \sum_{l=0}^{k-1} C_{jl}}{C_{jk}} (1 - e^{-\beta_0 i_{jk}})^{C_{jk}} (e^{-\beta_0 i_{jk}})^{S_j - \sum_{l=1}^{k} C_{jl}}} \right] \\
&= \sum_{j=1}^{m} \sum_{k=1}^{n_j} \left[C_{jk} \left(\log \frac{1 - e^{-\beta' i_{jk}}}{1 - e^{-\beta_0 i_{jk}}} \right) + \left(\sum_{l=1}^{k} C_{jl} - S_j \right) (i_{jk}(\beta' - \beta_0)) \right] \\
&= \sum_{j=1}^{m} \sum_{k=1}^{n_j} \left[C_{jk} \left(a_{jk} + \sum_{l=k}^{n_j} b_{jl} \right) - S_j b_{jk} \right],
\end{aligned}
\tag{17}
$$

where $a_{jk} = \log \frac{1 - e^{-\beta' i_{jk}}}{1 - e^{-\beta_0 i_{jk}}}$ and $b_{jk} = i_{jk}(\beta' - \beta_0)$.

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

$$\frac{\partial \log \lambda}{\partial C_{jk}} = a_{jk} + \sum_{l=k}^{n_j} b_{jl} \leqslant 0$$

$$\Leftrightarrow \beta' \sum_{l=k}^{n_j} i_{jl} + \log[1 - e^{-\beta' i_{jk}}] \leqslant \beta_0 \sum_{l=k}^{n_j} i_{jl} + \log[1 - e^{-\beta_0 i_{jk}}],$$

(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.

which is true since $g_{jk}(\beta) = \beta \sum_{l=k}^{n_j} i_{jl} + \log[1 - e^{-\beta i_{jk}}]$ is a monotonic and increasing function of β.

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 β' tend to β_0 ($\beta' \uparrow \beta_0$), which results in:

$$a_{jk} + \sum_{l=k}^{n_j} b_{jl} = \left[\mathrm{Log}[1 - e^{-\beta' i_{jk}}] + \sum_{l=k}^{n_j} i_{jl}\beta' \right]$$
$$- \left[\mathrm{Log}[1 - e^{-\beta_0 i_{jk}}] + \sum_{l=k}^{n_j} i_{jl}\beta_0 \right]$$
$$\approx (\text{via Taylor expansion})$$
$$(\beta' - \beta_0)\left(\frac{i_{jk}}{e^{\beta_0 i_{jk}} - 1} + \sum_{l=k}^{n_j} i_{jl} \right) = (\beta' - \beta_0)r_{jk}, \quad (18)$$

where $r_{jk} = \left(\frac{i_{jk}}{e^{\beta_0 i_{jk}} - 1} + \sum_{l=k}^{n_j} i_{jl} \right)$. Hence, $\log \lambda$ becomes:

$$\log \lambda = \sum_{j=1}^{m} \sum_{k=1}^{n_j} [C_{jk}((\beta' - \beta_0)r_{jk}) - S_j i_{jk}(\beta' - \beta_0)], \quad (19)$$

which determines the form of the test for the upper limit (since all other factors are independent of β_0):

$$\Psi = \begin{cases} 1 \text{ if } \sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} \leqslant d \\ 0 \text{ if } \sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} > d \end{cases} \quad (20)$$

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 β_0 for which holds:

$E(\Psi) = 0.025$, and

$$\sum_{j=1}^{m} \sum_{k=1}^{n_j} C_{jk} r_{jk} = d.$$

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