Logistic Growth Models for Estimating Vaccination Effects In Infectious Disease Transmission Experiments

by

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ABSTRACT

LOGISTIC GROWTH MODELS FOR ESTIMATING VACCINATION EFFECTS IN INFECTIOUS DISEASE TRANSMISSION EXPERIMENTS

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Veterinarians often perform controlled experiments in which they inoculate animals with infectious diseases. They then monitor the transmission process in infected animals. The aim of such experiments can be to assess vaccine effects. The fitting of individual-level models (ILMs) to the infectious disease data, typically achieved by means of Markov Chain Monte Carlo (MCMC) methods, can be computationally burdensome. Here, we want to see if a vaccination effect can be identified using simpler regression-type models rather than the complex infectious disease models. We examine the use of various logistic growth curve models, via a series of simulated experiments in which the underlying true model is a mechanistic model of infectious disease spread. We want to investigate whether a vaccination effect can be identified when only partial epidemic curves are observed, and to assess the performance of these models when experiments are run with various sets of observational times.

Contents

List of Tables

List of Figures

Chapter 1

Introduction

Infectious diseases are disorders caused by microorganisms, such as bacteria, viruses, parasites and fungi. Epidemics of infectious diseases can pose great risks to public health and economic growth. According to Statistics Canada, influenza and pneumonia are the leading causes of death from infectious diseases in Canada. Healthcare associated with infectious diseases cost between $453 million and $1 billion annually reported by The Public Health Agency of Canada (CADTH, 2012).

Vaccination has been proven to be an effective method of preventing certain diseases. Disease such as smallpox is eradicated worldwide (World Health Organization [WHO], 2012). The prevalence of polio is significantly reduced due to development of vaccination (Aylward, 2006). There are experiments conducted aiming to verify whether a proposed vaccine can provide protection against infection and to estimate vaccine efficacy.

Mathematical models can be used to understand the process of disease progression and to provide theoretical and empirical basis for control strategies. Stochastic epidemic models can incorporate the mechanism of disease spread, but the fitting of such models becomes computationally complex when infection processes are not fully observed.

The infectious disease transmission modeling framework used in this paper is that of the Individual Level Models (ILMs). Two studies are carried out based on the same experimental "layout" – a simulated experiment consists of ten pens, animals in five randomly selected pens are vaccinated. In Study 1, animals are assumed to be in isolated pens between which infection cannot transmit. In Study 2, an animal can be infected by animals in different pens. The simulated epidemic data are fitted to selected growth curve models. We examine the performance of these models in identifying vaccination effects and see how models perform when using only partial epidemic curves.

Chapter 2

Logistic Growth Models for Estimating Vaccination Effects In Infectious Disease Transmission Experiments

This chapter contains a manuscript to be submitted to a peer-reviewed journal.

2.1 Introduction

Infectious diseases affect humans, animals, and plants worldwide and can have high health, social and economic impacts. For instance, the 2009 influenza pandemic that initially broke out in Mexico and spread globally was caused by a strain of virus

that has killed more than 18,000 people since it first appeared (WHO, 2010). During the course of the 2001 foot and mouth (FMD) outbreak that occurred in the UK, approximately 4,200,000 animals were slaughtered. It is estimated that due to the 2001 FMD outbreak, the UK's tourism industry lost between C$4.91 - 7.36 billion, and the agriculture industry lost between C$1.96 - 5.89 billion (Public Safety Canada, 2006).

The efforts to gain understanding of these types of epidemics increasingly draw on the use of mathematical models to locate and track the mechanism of how the disease spreads and to evaluate the potential impact of control programs.

Individual-level models (ILMs) are classes of models that can be applied to epidemic data to aid in the understanding of the dynamics of infectious disease spread among heterogeneous populations (Deardon et al., 2010). These models are both highly flexible and intuitive. However, the fitting of such models to infectious disease data, typically done in a Bayesian Markov chain Monte Carlo (MCMC) framework, is generally highly computationally burdensome (e.g. Deardon et al., 2010).

An approach that is often taken when modeling infectious disease data, certainly in agricultural and veterinary situations, is to use growth curve models (Madden et al., 2007). While such models do not account for the mechanism of disease spread, and so are unlikely to give as good a fit to the data as more mechanistic infectious disease models, they are still used to identify treatment effects (Seber & Wild, 1989). We examine the use of such growth curve models in the context of a series of simulated

experiments in which the underlying true model is in fact a mechanistic model of infectious disease spread.

Disease transmission experiments can be performed in a controlled environment in which an animal is inoculated with an infectious disease agent and then the disease transmission process is observed on the entire population. Many of these experiments are aimed to assess the effect of vaccines. Examples of such experiments include one exploring vaccination against Aujeszky's disease virus (ADV) in pigs (De Jong & Kimman, 1994) and classical swine fever virus transmission experiment (Dewulf et al., 2001).

When designing such experiments, choices must be made regarding the size and duration of an experiment. Often, these choices are guided only by intuition and resource constraints (Cook et al., 2008), and observations may be made more often than they need to be. Here, we explore the question of whether frequent sampling is necessary for modeling the epidemic process when we are interested in identifying the effect of a vaccination.

The purposes of this study are to show if vaccine effects can be identified using simpler regression-type models rather than complex dynamic infectious disease models such as ILMs, to show if a vaccination effect can be identified when only partial epidemic curves are observed, and to examine the effect of using different observation points (designs) for given experiments. The paper is laid out in the following way. The infectious disease model framework is outlined in Section 2.3. Section 2.4 introduces

the experiments conducted and the epidemic simulation. Section 2.5 presents the criteria for assessing models and designs. Section 2.6 and Section 2.7 present the various growth models used and growth model selection results. Section 2.8 shows the results from experiments run with different sets of observational times. Finally, a discussion is presented in Section 2.9. The appendix contain all results.

2.2 Infectious Disease Model Framework

The infectious disease transmission modeling framework used in this paper is that of the individual-level models (ILMs) described in Deardon et al. (2010). The models are placed within an SIR compartmental framework that can be summarized as follows. We assume that at discrete time point t, $t = 1...t_{max}$, where t_{max} is the length of the epidemic, and each individual may be in one of three states:

- Susceptible (S), in which an individual without disease may contract the disease;
- Infectious (I), in which an individual has contracted the disease and can transmit it;
- Removed (R), meaning that the individual has been removed from the population, perhaps because of death from the disease, as a result of being isolated from the susceptible population, or having recovered and developed immunity to the disease.

In this model, an individual either remains susceptible throughout the time period studied or moves through the states S $\rightarrow$ I $\rightarrow$ R. Individuals move from I $\rightarrow$ R depending upon the infectious period γ_I, the time interval that determines how long an individual can transmit the disease before being removed. In this study, we assume a fixed infectious period for all individuals.

The probability that a previously susceptible individual i first becomes infectious at time $t+1$ is given in the general form of Deardon et al. (2010) by

$$P(i,t) = 1 - \exp\left[\left\{-\Omega_S(i)\sum_{j\in I(t)}\Omega_T(j)K(i,j)\right\} + \varepsilon(i,t)\right] \tag{2.1}$$

where $I(t)$ is the set of infectious individuals at time t; $\Omega_S(i)$ is a susceptibility function representing the potential risk factors associated with susceptible individual i contracting the disease; $\Omega_T(j)$ is a transmissibility function representing potential risk factors associated with infectious individual j spreading the disease; $K(i,j)$ is an infection kernel representing potential risk factors shared between both susceptible and infectious individuals; and $\varepsilon(i,t)$ represents some random factors that are not explained by the basic framework of the model.

2.3 Data Simulation

The purpose of the vaccination study considered here is to assess the effectiveness of a vaccine for both protecting an individual against infection and restricting the spread of disease. We assume our vaccine is not fully effective, in this case meaning

that vaccinated individuals may still get infected, but at a lower rate of infection. Two studies are carried out based on the same experimental "layout". The simulated experiment consist of ten pens, each containing 20 small animals (e.g. chickens). Five pens are randomly selected and animals in the pen are vaccinated. At time 1, a single animal in each pen is infected. The length of the experimental observation period t_{max} is set to be 20. During data simulation, ILM parameters values result in wide range of pen-level epidemics. For example, in some pens all animals are infected before t= 20, in some only a portion.

2.3.1 Study 1, Isolated Pens

The probability of a susceptible individual i being infected at time t is given by:

$$P(i,t) = 1 - \exp\left\{ -(\alpha_0 + \alpha_1 V_i) \sum_{j \in I(t) \cap \phi(i)} 1 \right\} \tag{2.2}$$

where α_0, $\alpha_1 > 0$, V_i= $\begin{cases} 1 & \text{if } i \text{ is NOT vaccinated} \\ 0 & \text{if } i \text{ is vaccinated} \end{cases}$, and $\phi(i)$ is the set of infectious individuals in the same pen as individual i. When an animal is not vaccinated, it has a susceptibility of $\alpha_0 + \alpha_1$, whereas a vaccinated animal has a reduced susceptibility of α_0. Since the individuals are considered to be in an isolated pen, the probability of infection at any given time depends only on vaccination status and number of infectious individuals within the same pen.

2.3.2 Study 2, Allow Infection Among Pens

Here, the probability of a susceptible individual i being infected at time t is given by:

$$P(i,t) = 1 - \exp\left\{ - \left[\left((\alpha_0 + \alpha_1 V_i) \sum_{j \in I(t) \cap \phi(i)} 1 \right) + \left((\beta_0 + \beta_1 V_i) \sum_{j \in I(t) \setminus \phi(i)} 1 \right) \right] \right\} \tag{2.3}$$

where α_0, α_1, β_0, $\beta_1 > 0$, and $V_i = \begin{cases} 1 & \text{if } i \text{ is NOT vaccinated} \\ 0 & \text{if } i \text{ is vaccinated} \end{cases}$

In addition to the α terms representing susceptibility within the same pen, the term $\beta_0 + \beta_1 V_i$ is introduced to represent the infective pressure exerted on the susceptible individual i by infectious individuals in other pens ($I(t) \setminus \phi(i)$). If individual i is not vaccinated, its rate of infectivity is increased by $\beta_0 + \beta_1$ for each infected animal in other pens at time t; if the individual i is vaccinated, its rate of infectivity is increased by β_0 for each infected animal in other pens at time t.

2.4 Evaluation Criteria for Model and Design Selection

$\boldsymbol{L^{(0,T)}}$, $\boldsymbol{L^{(1,T)}}$: Baseline time to 50% infection ($LT_{(50)}$) for vaccinated and non-vaccinated animals, respectively

Experiment r produces data, the time at which an individual become infectious: $x(r,k,t)$, where r is the experiment number, k is the pen, t is the time, $t \in \{\tau_1, ..., \tau_n\}$ and τ_1,...,τ_n are the observation times. For each experiment, r=1,...,1000, for each

pen k=1,...,10, and observation times $t \in \{1, 2, 3, ..., 20\}$, we find $LT_{(50)}(r, k) = min(t)$ s.t. $\sum_{(x(m,k,t)\leq t)} 1 \geq 10$, i.e. the time at which at least 50% of animals in pen k are infected. These 1000 experimental epidemics are used in order to find a Monte Carlo estimate of the "true" average $LT_{(50)}$ of pens of vaccinated and non-vaccinated animals, respectively.

$$L^{(0,T)} = \left(\frac{1}{1000}\right)\left(\frac{1}{5}\right)\sum_{r=1}^{1000}\sum_{k\in V(r,k)^{(0)}} LT_{(50)}(r, k) \tag{2.4}$$

where $V(r, k)^{(0)}$ is the set of pens of vaccinated animals in experiment r, and

$$L^{(1,T)} = \left(\frac{1}{1000}\right)\left(\frac{1}{5}\right)\sum_{r=1}^{1000}\sum_{k\in V(r,k)^{(1)}} LT_{(50)}(r, k) \tag{2.5}$$

where $V(r, k)^{(1)}$ is the set of pens of non-vaccinated animals in experiment r. For calculating $L^{(0,T)}$, $L^{(1,T)}$, we used fully observed epidemics (i.e. $x(r, k, t)$ for $t \in \{1, 2, 3, ..., 20\}$). When assessing model performance at different sets of time points, we used systematic partial designs, i.e. observation times spaced by equal intervals. e.g., $t \in \{2, 4, 6, ..., 20\}$, $t \in \{3, 6, 9, ..., 18\}$, $t \in \{4, 8, 12, ..., 20\}$, etc.

$\boldsymbol{L^{(0,E)}}$, $\boldsymbol{L^{(1,E)}}$: Estimated $LT_{(50)}$ for vaccinated and non-vaccinated animals, respectively

For each experiment m=1,...,50, for each pen k=1,...,10, and observation time $t \in \{\tau_1, ..., \tau_n\}$, we find $N(m, k, t)$=$\sum_{(x(m,k,t)\leq t)} 1$, the cumulative number of infections at each observation time t.

The relationship between the response variable $N(m,k,t)$ and explanatory variables, t and $V(m,k)$, is modeled by fitting each of the logistic growth curve models shown in equation 2.11 to 2.14 on page 13. Parameter estimates $\hat{\theta}$ obtained are used to calculate the estimated $LT_{(50)}$ values under the logistic models; $L_m^{(0,E)}$, $L_m^{(1,E)}$ denote the estimated $LT_{(50)}$ values for vaccinated and non-vaccinated pens, respectively, for experiment m.

We then calculate:

$$\lambda^T = L^{(0,T)} - L^{(1,T)} \tag{2.6}$$

and

$$\lambda_m^E = L_m^{(0,E)} - L_m^{(1,E)} \tag{2.7}$$

Thus, λ^T, λ_m^E represent the true and estimated difference in $LT_{(50)}$ values between vaccinated animals and non-vaccinated animals, respectively.

Finally, we use the following metrics to ascertain how well the vaccine effect is estimated under a given model and design (i.e. set of observation times):

$$d_1 = \frac{1}{50}\sum_{m=1}^{50}\left(\lambda^T - \lambda_m^E\right)^2 \tag{2.8}$$

$$d_2 = \frac{1}{50}\sum_{m=1}^{50}\left(L^{(0,T)} - L_m^{(0,E)}\right)^2 \tag{2.9}$$

$$d_3 = \frac{1}{50}\sum_{m=1}^{50}\left(L^{(1,T)} - L_m^{(1,E)}\right)^2 \tag{2.10}$$

Thus, d_1 represents the mean squared deviation (MSD) between the true $LT_{(50)}$ difference due to vaccination and the estimated $LT_{(50)}$ difference due to vaccination over 50 replicates of the experiment; and d_2 and d_3 are the MSD between the true $LT_{(50)}$ and the estimated $LT_{(50)}$ values for vaccinated and non-vaccinated animals, respectively. The average BIC values are also obtained and used as a criterion for model selection.

2.5 Growth Model Selection

A growth curve is an empirical model of the evolution of a quantity against time or against some other factors (Seber & Wild, 1989). We can incorporate the mathematical relationships between the model parameters and a treatment covariate into the growth curve models and fit the observed data directly. Alternatively, we can estimate the parameters in the model separately for each individual treatment and then investigate their relationships with treatment (van Maanen & Xu, 2003).

Various growth curves were considered as models for the epidemic curves observed in the simulated experiments. These include the three-parameter logistic, Weibull and Richard's growth models (Seber & Wild, 1989). Models of best fit to the observed data are obtained from minimizing the residual sums of squares (RSS) using the `nls` package in R. Similar results were observed for the logistic, Weibull and Richard's growth curve models. Here, therefore we merely present results for the logistic growth curve models used as shown in equations 2.11 to 2.14:

Model 1, standard model with vaccination effect:

$$N(m,k,t) = \frac{\theta_1}{1+\exp\{-[\theta_2+\theta_3(t-1)+\theta_4 V(m,k)]} + \varepsilon(k,t) \tag{2.11}$$

Model 2, asymptote vaccine effect is included in the model:

$$N(m,k,t) = \frac{\theta_1+\theta_5 V(m,k)}{1+\exp\{-[\theta_2+\theta_3(t-1)+\theta_4 V(m,k)]} + \varepsilon(k,t) \tag{2.12}$$

Model 3, time-vaccination effect interaction included in the model:

$$N(m,k,t) = \frac{\theta_1}{1+\exp\{-[\theta_2+\theta_3(t-1)+\theta_6(t-1)V(m,k)+\theta_4 V(m,k)]} + \varepsilon(k,t) \tag{2.13}$$

Model 4, vaccinated and non-vaccinated data fitted separately using basic logistic model:

$$N(m,k,t) = \frac{\theta_1}{1+\exp\{-[\theta_2+\theta_3(t-1)]} + \varepsilon(k,t) \tag{2.14}$$

In each model, θ_1 is the upper asymptote, θ_3 is a rate parameter, $\varepsilon(k,t)$ is the error term and is assumed to follow a normal distribution with mean 0 and some unknown standard deviation σ.

2.5.1 Mixed Effects Models

These four nonlinear regression models allow for one source of randomness: the additive error term, $\varepsilon(k,t)$. We also want to determine whether the model will be improved if adjusted to account for variation among pens. In a real-life experiment, this variation can be thought of as a result of unobservable changes in the environment of the pen that occur at random (Rits & Streibig, 2008), e.g. health of the animals may be different in different pens. In our simulated experiments, this variation could be thought of as resulting from variation due to early-stage random fluctuations that cannot be captured by the general growth curve structure. For such nonlinear mixed models, this randomness can be quantified in terms of random effects. A choice needs to be made about on which parameters this variation manifests itself. Variation across pens may exist for all parameters in the model or may only show up in a few or a single parameter.

For each logistic model, five different mixed effect models are tested, each with the same fixed effects parameters (θ_1, θ_2, θ_3, etc.), but different random-effects. M_1 represents the model with random effects only assigned to the parameter θ_1, but not to other parameters. M_2 represents random effects part of the model only assigned to θ_2, and so on, up to M_4 which has random effects assigned to θ_4. Note that we do not consider random effects on θ_5 and θ_6 for reasons of brevity. M_{all} has random effects specified for parameters θ_1 to θ_4 and M_0 represents the model that does not consider any random effect. In all cases, the random effects are assumed to be normally

distributed with mean 0 and an unknown variance σ^2_{pen}. Mixed effects models are fitted in R using the function `nlme` and models without random effects are fitted by using the function `nls`.

2.5.2 Study 1, Isolated Pens

First, we consider Study 1 where animals are assumed to be in isolated pens between which infection cannot transmit. ILM parameter values are chosen so that there is both an obvious observed difference between the epidemic curves of the vaccinated and non-vaccinated pens of animals, and such that "informative" epidemic curves tend to be produced by the end of an experiment at $t = 20$ (i.e. the infection process does not claim all animals very quickly, nor does the infection fail to get going by $t = 20$). Specifically, parameter values are set to: $\alpha_0 = 0.02$, $\alpha_1 = 0.04$ and $\gamma_I = 10$. In Study 1, infection in 131 out of the (5*1000=) 5000 vaccinated pens in which disease was simulated did not reach 50% and these are thus excluded in the calculation of $L^{(0,T)}$. The 1,000 "baseline" simulations resulted in estimates of: $L^{(0,T)} = 10.4302$ for pens of vaccinated animals, and $L^{(1,T)} = 5.22860$ for pens of non-vaccinated animals, and so here, $\lambda^T = L^{(0,T)} - L^{(1,T)} = 5.2016$.

2.5.3 Study 2, Allow Infection Among Pens

Now, we consider Study 2 where an animal can be infected by animals in different pens, as well as those in their own pen. ILM parameter values are set to: $\alpha_0 = 0.02$

, $\alpha_1 = 0.04$, $\beta_0 = 0.001$, $\beta_1 = 0.002$ and $\gamma_I = 10$. The 1,000 "baseline" simulations resulted in estimates of: $L^{(0,T)} = 6.8756$ for pens of vaccinated animals, $L^{(1,T)} = 4.336$ for pens of non-vaccinated animals, and so here, $\lambda^T = L^{(0,T)} - L^{(1,T)} = 2.5396$.

2.6 Model Selection: Fixed or Mixed Effects Models

Fifty epidemic data sets generated using the ILM, are fitted to each of the logistic models described previously. For various forms of Model 1, the results of the averaged BIC, d_1, d_2, d_3 criteria and the corresponding standard errors across the 50 epidemic replications are shown in Table 2.1 for Study 1 and in Table 2.2 for Study 2. For both studies, M_{all} results in the lowest BIC value. However, the deviations between the estimated and true $LT_{(50)}$ values, d_1, d_2, and d_3, show that M_{all} is not the best at estimating the vaccination effect on the $LT_{(50)}$. For Study 1, M_4 produces the lowest average d_1 value but M_0 performs approximately as well as M_4. For Study 2, M_2, M_4, and M_0 all perform approximately equivalently, each producing relatively low d_1 and d_2 values. In both studies, M_3 and M_{all} have much larger d_1, d_2, and d_3 values, and also larger corresponding standard errors. This shows including random effects can appear to improve model fit according to the BIC, but it can be an illusion. It appears that θ_3 random effects are absorbing important traits of the epidemic process and masking the vaccination effects we are interested in.

For Model 4, each epidemic data set is split by vaccination status, and then the vaccinated and non-vaccinated data are fitted separately using the various mixed (and fixed) effects logistic models. The results of the averaged BIC and d_1, d_2, and d_3 values are shown in Table 2.3 for Study 1 and in Table 2.4 for Study 2. The close values of d_1, d_2, d_3 and their corresponding standard errors indicates that the models perform approximately as well as any other, but that including random effects seems unnecessary. Given this, M_0, the model with no random effects, is chosen for all further analyses.

Finally, note that results are not shown for the various mixed-effects variants of models 2 and 3 because it was found difficult to fit those models in the automated way required for our simulation study; often in these cases the `nlme` function in R appeared to be very sensitive to starting values.

Table 2.1: Study 1, Comparing fixed and mixed effects variants of Model 1

	M_1	M_2	M_3	M_4	M_{all}	M_0
BIC	897.5940	835.5292	614.4752	1007.1861	587.8078	1020.18
d_1	3.1995	3.2552	34.3909	2.8922	30.766	2.9123
$se(d_1)$	(0.4779)	(0.5715)	(1.2314)	(0.5599)	(4.0003)	(0.5990)
d_2	3.5329	2.4975	23.8556	2.2182	20.7583	2.2023
$se(d_2)$	(0.3718)	(0.4870)	(0.7383)	(0.4414)	(1.9674)	(0.4395)
d_3	0.28433	0.53301	1.25422	0.64825	5.9356	0.6887
$se(d_3)$	(0.05238)	(0.09393)	(0.16500)	(0.10696)	(1.97571)	(0.10805)

Table 2.2: Study 2, Comparing fixed and mixed effects variants of Model 1

	M_1	M_2	M_3	M_4	M_{all}	M_0
BIC	755.9508	638.3973	629.1175	737.2766	536.1441	728.8671
d_1	0.2279	0.2022	3.4903	0.2064	2.4841	0.2065
$se(d_1)$	(0.04564)	(0.0431)	(0.5026)	(0.04248)	(0.38588)	(0.04307)
d_2	0.5483	0.4361	2.7624	0.4654	2.3943	0.4652
$se(d_2)$	(0.07961)	(0.07048)	(0.35437)	(0.07394)	(0.35687)	(0.07393)
d_3	0.2744	0.2825	0.2847	0.2896	0.40026	0.3017
$se(d_3)$	(0.03428)	(0.0338)	(0.0423)	(0.03452)	(0.08219)	(0.03517)

Table 2.3: Study 1, Comparing fixed and mixed effects variants of Model 4

	M_1	M_2	M_3	M_{all}	M_0
BIC_{vac}	417.273	359.157	334.3364	327.8443	515.036
BIC_{nonvac}	410.8457	234.4853	332.4152	249.9591	411.0354
d_1	2.1048	3.3222	2.355	2.5273	2.3027
$se(d_1)$	(0.4947)	(0.6201)	(0.5852)	(0.5012)	(0.5255)
d_2	1.9795	2.7122	2.2208	2.4287	1.9923
$se(d_2)$	(0.3587)	(0.5593)	(0.3983)	(0.4717)	(0.4061)
d_3	0.5361	0.4107	0.5848	0.5462	0.4977
$se(d_3)$	(0.0854)	(0.07452)	(0.08448)	(0.09346)	(0.08261)

Table 2.4: Study 2, Comparing fixed and mixed effects variants of Model 4

	M_1	M_2	M_3	M_{all}	M_0
BIC_{vac}	353.4309	279.7892	304.5836	281.4607	356.9674
BIC_{nonvac}	302.8916	251.0889	302.9612	210.893	298.356
d_1	0.2954	0.285	0.3114	0.3217	0.2911
$se(d_1)$	(0.0525)	(0.05088)	(0.05211)	(0.0551)	(0.05178)
d_2	0.5936	0.5502	0.6367	0.6319	0.5754
$se(d_2)$	(0.09811)	(0.09169)	(0.10158)	(0.10233)	(0.09568)
d_3	0.2314	0.2269	0.231	0.2334	0.231
$se(d_3)$	(0.02972)	(0.02949)	(0.02965)	(0.03062)	(0.02965)

2.7 Results: Comparison of Designs and Fixed Effects Models.

In total, 37 designs were evaluated under each of the four fixed effects models. Results for the 37 designs are shown in Appendix A for Study 1, and Appendix B for Study 2. Here, only a representative selection of designs are discussed for the purpose of brevity.

2.7.1 Study 1, Isolated Pens

Here we present results of selected designs for Study 1, which uses isolated pens. Results for logistic Model 1 are shown in Table 2.5.

As the number of observational points decreases, the mean standard error of vaccination parameter $se(\theta_4)$ increases indicating decreasing precision. Bias in the estimation of vaccination effect is reflected by values of d_1, d_2 and d_3. Here we evaluate model performance primarily by d_1. As the starting observation time in the design increases, the model appears to have difficulty identifying the rate of epidemic for the non-vaccinated data, reflected by the increasing d_3 value in Table 2.5. Since early time points contain more information in terms of the epidemic progress for the non-vaccinated data, designs with first observation time point of 4 or later have larger d_1 and d_3 values than designs with an earlier starting point. If Model 1 is used to assess the epidemic progress, including time point 1 or 2 appears to be essential.

Table 2.5: Model 1, Study 1

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,2,3,4 ,..., 20)	0.2602	2.9124	2.2024	0.6887
	(0.4204)	(0.599)	(0.4395)	(0.1081)
(2,8,14,20)	1.0055	2.6126	3.1745	0.3609
	(3.2664)	(0.4933)	(0.5326)	(0.0466)
(3,8,13,18)	0.6712	2.9395	2.5529	0.3914
	(1.1272)	(0.5448)	(0.4358)	(0.0844)
(4,8,12,...,20)	0.4703	5.4189	2.4312	1.9523
	(0.7094)	(1.0422)	(0.4773)	(0.3297)
(5,8,...,17,20)	0.4081	12.8967	2.3562	8.514
	(0.6676)	(2.1148)	(0.4968)	(1.2257)
(6,8,...,18,20)	0.4605	30.0143	2.2065	25.7436
	(1.1902)	(4.264)	(0.464)	(3.3439)

This is illustrated by the plot of the data from a single epidemic along with fitted Model 1 for designs $t = (3, 8, 13, 18)$, $t = (4, 8, 12, 16, 20)$ and $t = (5, 8, 11, 14, 17, 20)$, shown in Figure 2.1.

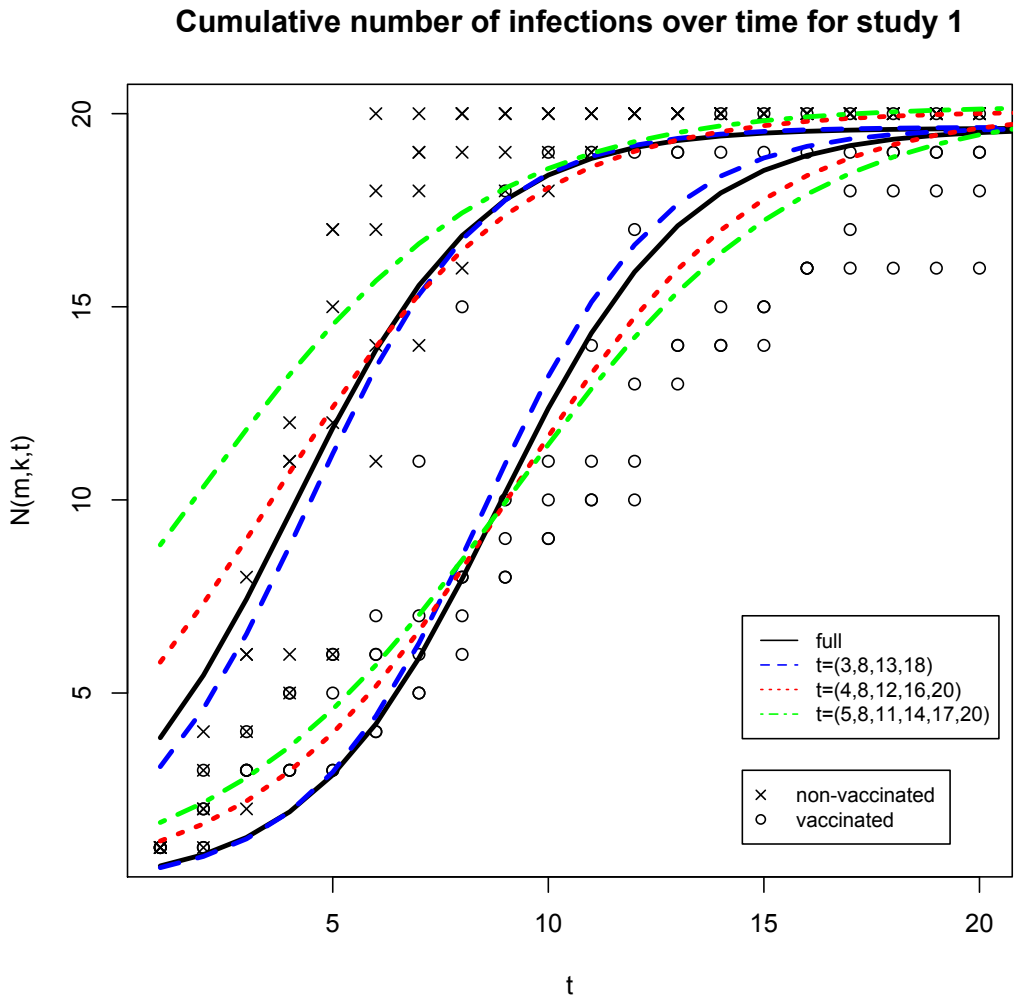

Figure 2.1: Data from various designs are fitted by Model 1. Full design plotted in black, design t=(3,8,13,18) plotted in blue, design t=(4,8,12,16,20) plotted in red, design t=(5,8,11,14,17,20) plotted in green.

Results for Model 2 are shown in Table 2.6.

Table 2.6: Model 2, Study 1

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,2,3,...,20)	0.2794	0.6016	1.7439	2.1108	0.506
	(0.5821)	(1.0784)	(0.3565)	(0.3209)	(0.0849)
(2,8,14,20)	0.9679	1.1572	1.7201	2.8001	0.3518
	(3.0299)	(2.5974)	(0.3134)	(0.3457)	(0.0526)
(3,8,13,18)	0.7532	1.3161	2.0402	2.5003	0.305
	(1.6955)	(3.1687)	(0.3918)	(0.3391)	(0.0633)
(4,8,12,...,20)	0.537	1.2422	2.4171	2.1244	0.8479
	(1.0839)	(3.246)	(0.6032)	(0.3804)	(0.175)
(5,8,11,14,17,20)	0.452	1.3403	4.829	2.0538	3.3384
	(0.9047)	(6.161)	(1.2379)	(0.442)	(0.6009)
(6,8,10,...,18,20)	0.4565	1.3746	12.2341	1.9434	11.1353
	(1.032)	(6.0627)	(2.2019)	(0.411)	(1.7511)

The results show that d_1 becomes larger as the first observation time increases in a similar manner seen for Model 1. However, d_1 and d_3 values are much smaller than values seen under the previous model. Therefore, adding a parameter to represent the difference in asymptote between vaccinated and non-vaccinated pens seems to improve the fit of the model.

Results for Model 3 are shown in Table 2.7.

Table 2.7: Model 3, Study 1

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,2,3,...,20)	0.4272	0.0996	2.7604	2.2063	0.5033
	(0.6981)	(0.1751)	(0.5872)	(0.4473)	(0.0831)
(2,8,14,20)	1.3986	0.8268	2.9937	2.406	0.7225
	(21.8467)	(22.5028)	(0.5009)	(0.5278)	(0.1319)
(3,8,13,18)	1.2147	0.4549	2.8658	2.2538	0.5834
	(7.3602)	(4.0252)	(0.5422)	(0.4542)	(0.103)
(4,8,12,...,20)	1.6572	0.4984	3.139	2.4113	0.5491
	(9.9775)	(3.4941)	(0.7416)	(0.49)	(0.0933)
(5,8,11,...,20)	3.1303	0.7592	3.5109	2.3578	0.6682
	(29.9686)	(7.5665)	(1.2573)	(0.5066)	(0.2242)
(6,8,10,...,20)	4.7595	0.9358	3.311	2.2587	0.6861
	(31.7391)	(6.4047)	(1.1068)	(0.4731)	(0.2155)

For Model 3, the non-linear least squares algorithm is sensitive to starting values of the parameters chosen. It therefore appears that the model fitting becomes unstable due to increased number of parameters in the model. Results were not obtained for designs with second time point of 9 and above (more than 10 out of 50 epidemics can not be fitted for these designs). Considering the results for designs with observation time starting at 5 or 6 in Table 2.7 (and also Table A.12), d_1 values are generally smaller than values of the previous two models. Therefore, adding a vaccination

parameter θ_6 to account for the difference in infection rate would appear to improve the ability to estimate the vaccination effect on the $LT_{(50)}$ for such designs.

Figure 2.2 shows the plot of the fitted model for designs $t = (4, 9, 14, 19)$, $t = (5, 9, 13, 17)$ and $t = (6, 9, 12, 15, 18)$. For this particular epidemic, at time 9, total number of infected animals are (16,19,20,20,20) for non-vaccinated pens. Both designs result in similar fits to the full design, also illustrating that Model 3 is not particularly sensitive to the choice of the first observation point.

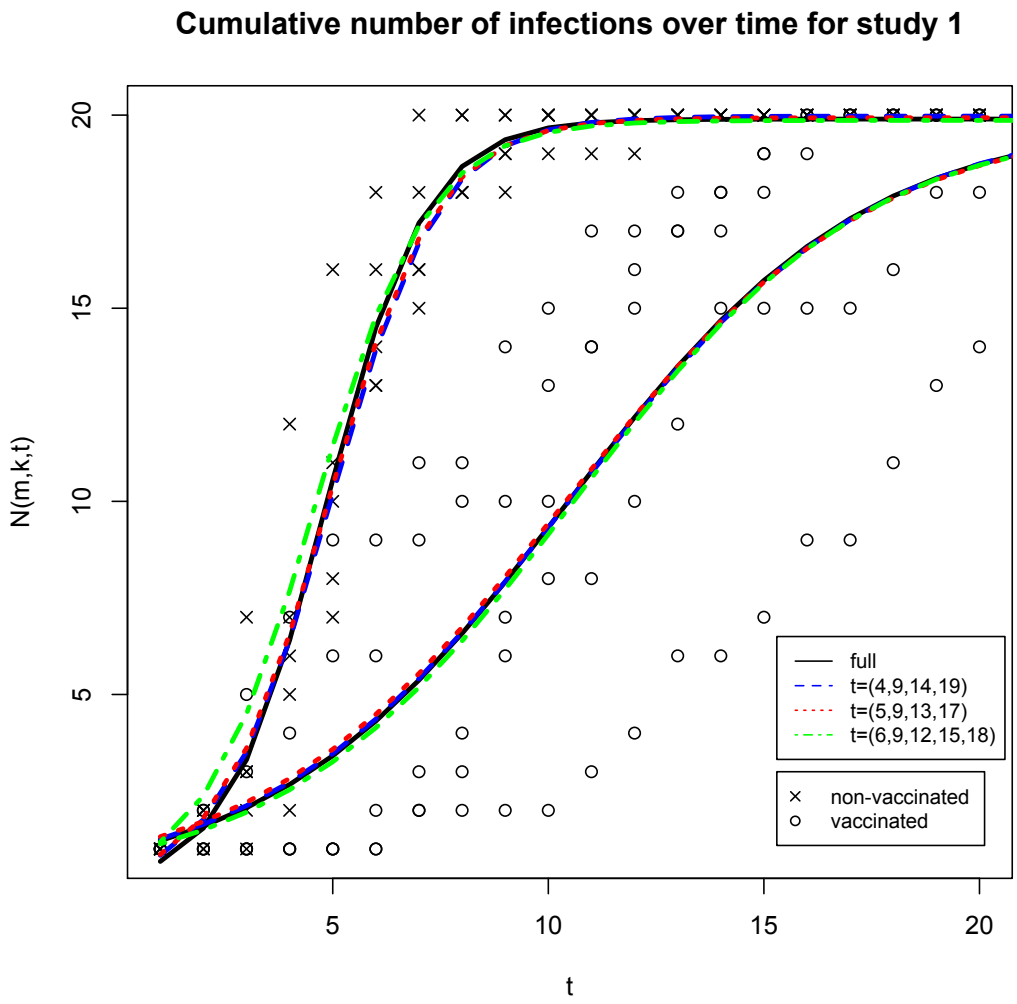

Figure 2.2: Data from various designs are fitted by Model 3. Full design plotted in black, design t=(4,9,14,19) plotted in blue, t=(5,9,13,17) plotted in red, t=(6,9,12,15,18) plotted in green

Table 2.8: Model 4, Study 1

time points	d_1	d_2	d_3
(1,2,3,...,20)	2.3027	1.9923	0.4977
	(0.5255)	(0.4061)	(0.0826)
(2,8,14,20)	2.4229	2.1267	0.7895
	(0.4311)	(0.4813)	(0.185)
(3,8,13,18)	2.3155	1.9931	0.6437
	(0.4697)	(0.398)	(0.1227)
(4,8,12,...,20)	2.4572	2.0178	0.5872
	(0.6067)	(0.4015)	(0.0941)
(5,8,11,...,20)	3.0178	2.0823	0.7106
	(1.156)	(0.4393)	(0.2324)
(6,8,10,...,20)	3.0965	2.0231	0.8819
	(1.0394)	(0.4191)	(0.2774)

For Model 4, results are shown in Table 2.8. It is noted that d_1 and d_3 values for Model 4 appear to be less affected by the choice of first observation point than under the previous models. The models seem to give a similar fit under each design.

2.7.2 Study 2, Allow Infection Among Pens

Identical analyses are conducted for Study 2. Selected results are presented in Table 2.9 to 2.12 for Models 1 to 4, respectively.

Table 2.9: Model 1, Study 2

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,2,3,...,20)	0.1333	0.2942	0.5839	0.256
	(0.156)	(0.0516)	(0.097)	(0.0319)
(2,6,10,14,18)	0.4458	0.1826	0.5884	0.3535
	(1.4692)	(0.0332)	(0.0734)	(0.0373)
(3,6, 9,...,18)	0.2725	0.2895	0.5812	0.2441
	(0.3398)	(0.05)	(0.0905)	(0.0333)
(4,6,8,...,20)	0.1804	0.424	0.5578	0.7204
	(0.2265)	(0.0584)	(0.0915)	(0.102)

Figure 2.3 shows the plot of data from designs t=(2,6,10,14,18), t=(3,6,9,...,18), and t=(4,6,8,...,20) fitted by Model 1.

In this study, the four models seem to perform similarly whereas Model 3 and Model 4 have slightly more consistent d_1 values. Since the model of Study 2 includes the inter-pen effect, the infection process generally occurs at a faster rate (see Figure 2.3). By $t = 7$, non-vaccinated pens generally have an infected number of animals equal or close to 20. As a result, d_1 values are smaller in general compared to results of Study 1. Consider d_1 values for the full design and design with late starting obser-

Table 2.10: Model 2, Study 2

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,2,3,...,20)	0.1334	0.255	0.3012	0.6269	0.2427
	(0.1551)	(0.3303)	(0.0538)	(0.1016)	(0.0307)
(2,6,10,14,18)	0.3908	0.4839	0.1919	0.5993	0.3041
	(0.9571)	(0.6826)	(0.0363)	(0.0765)	(0.0324)
(3,6, 9,...,18)	0.2728	0.4857	0.2928	0.6212	0.2289
	(0.34)	(0.6713)	(0.0525)	(0.0946)	(0.0315)
(4,6,8,...,18,20)	0.1841	0.3598	0.3609	0.586	0.6084
	(0.2362)	(0.5524)	(0.0504)	(0.0947)	(0.0865)

Table 2.11: Model 3, Study 2

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,2,3,4,...,20)	0.2647	0.0746	0.2906	0.5674	0.2329
	(0.3399)	(0.0972)	(0.0513)	(0.0949)	(0.0298)
(2,6,10,14,18)	0.4858	0.1783	0.3228	0.609	0.4341
	(1.1081)	(1.2592)	(0.0519)	(0.1012)	(0.0558)
(3,6, 9,...,18)	0.8703	0.3609	0.2883	0.5774	0.3231
	(15.42)	(7.8029)	(0.0502)	(0.0965)	(0.0399)
(4,6,8,...,18,20)	1.1505	0.361	0.3228	0.5869	0.1793
	(13.3381)	(4.4834)	(0.0493)	(0.0957)	(0.025)

Table 2.12: Model 4, Study 2

time points	d_1	d_2	d_3
(1,2,3,4,...,20)	0.2911	0.5754	0.231
	(0.0518)	(0.0957)	(0.0297)
(2,6,10,14,18)	0.3223	0.6136	0.4156
	(0.0532)	(0.1018)	(0.0511)
(3,6, 9,...,18)	0.2909	0.5849	0.311
	(0.0507)	(0.0974)	(0.0378)
(4,6,8,...,20)	0.3203	0.5905	0.1835
	(0.0494)	(0.096)	(0.0257)

vation time, i.e. $t = 4$, small improvements in d_1 values are observed when additional vaccination parameters are added to the standard model (model 1) to account for difference in higher asymptote (model 2) and difference in rate of disease progress (model 3). This is due to the smaller difference in the disease progression rate among vaccinated and non-vaccinated pens for Study 2. Almost all vaccinated and non-vaccinated pens reach full infections by the end of observation period in Study 2. Whereas in Study 1, vaccinated pens do not reach full infection in some simulated experiments.

2.8 Conclusion

The goal of this article, as described in Section 1, is to investigate whether the effect of vaccination can be identified using logistic growth models and to see how models

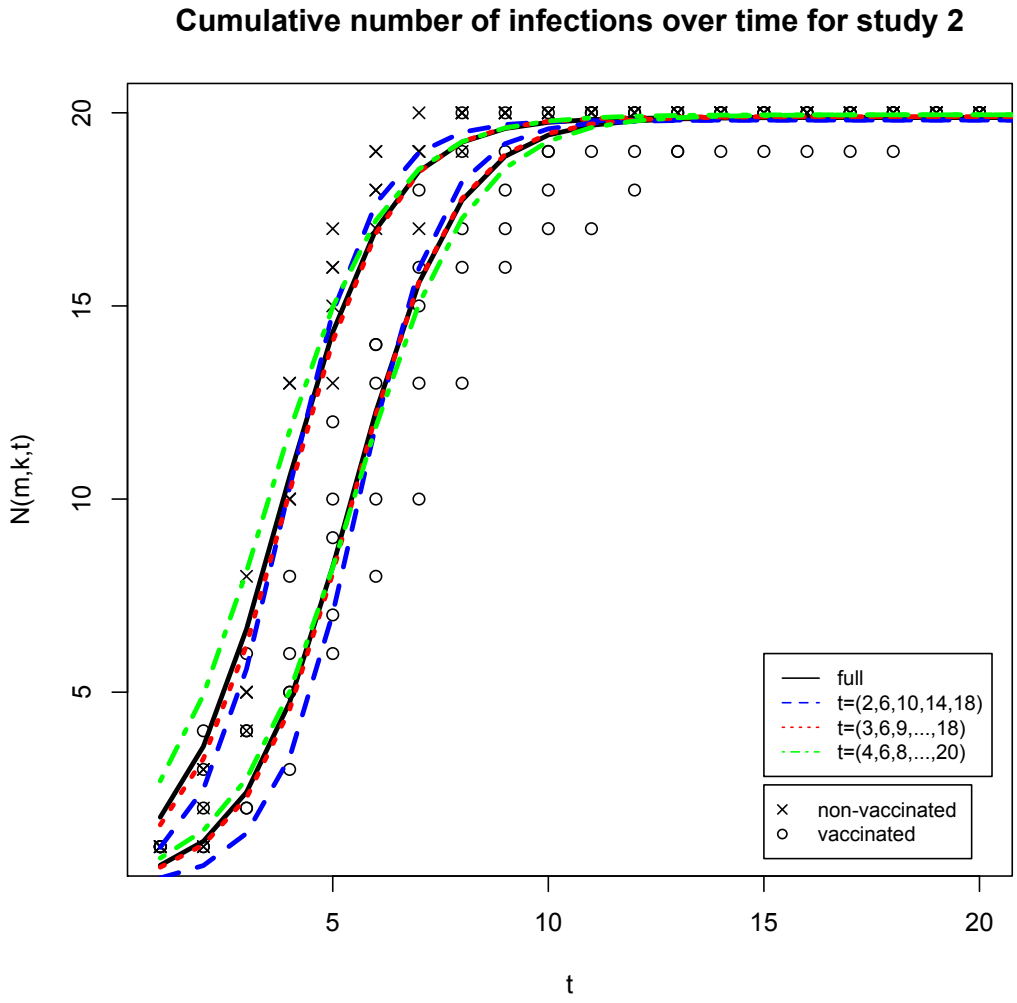

Figure 2.3: Data from various designs are fitted by Model 1. Full design plotted in black, design (t=2,6,10,14,18) plotted in blue, design (t=3,6,9,...,18) plotted in red, design t=(4,6,8,...,20) plotted in green

perform when only partially observed epidemic curves are used.

In both studies, we observe that as the first observation time point in the design increases, d_1 values increase for all models. This increase is most dramatic for Model

1 and Model 2. Model 2 seems to perform better than Model 1 which is reflected by lower d_1 values for the full design and designs with first observation times of 4 and above.

Results show that d_1 values are more consistent in Model 3 and Model 4. We observe that given many designs, Model 3 and Model 4 would fit similarly to data from the full design. Model 3 seems to perform as well as Model 4. The only disadvantage is that it is difficult to fit in R due to the extra parameter in the model.

In conclusion, logistic growth models can be used to identify vaccination effects with partially observed epidemics. Overall Model 4 seems to be the most robust among the four models with respect to consistency in d_1 values.

We now discuss some possible further work. One avenue would be to compare results achieved by fitting growth curves to those produced by fitting ILMs, perhaps by MCMC. This has not been considered here due to the extra computational burden exercised by such approaches.

For both simulation studies, the population is considered to be of the same condition except vaccination status. It would be well-reasoned to include heterogeneity between the pens. A question of interest here would be how to introduce random effects to the models in such a way that they allow for pen-level heterogeneity without distorting the underlying vaccination effect.

In Study 2, in which inter-pen infection occurs, we could consider location of the pens in the model so that animals of different pens exert different infective pressure

on susceptible animals depending on the distance between them.

Here, we have used arbitrarily chosen parameter values for our ILMs. It would be of interest to use values of parameters in the ILM for data simulation that mimic some real disease.

Finally, we could explore other experimental design problems, such as determining the number of animals that should be used in the experiment, the optimal duration of the study (e.g. Becker & Britton, 2001) and the ratio of initial number of susceptible and infectious animals (e.g. Velthuis et al., 2006) required for efficiently identifying vaccine effects.

Reference

Aylward, R. (2006). Eradicating polio: today's challenges and tomorrow's legacy. Ann Trop Med Parasitol, 100 (5-6): 401-13

Becker, N.G., & Britton, T. (2001). Design issues for studies of infectious diseases. Journal of Statistical Planning and Inference, 96(1), 41-66

Canadian Agency for Drugs and Technologies in Health (CADTH). Infectious Diseases. Retrieved from http://www.cadth.ca/priorities/-infectious-diseases

Cook, A. R., Gibson, G. J., & Gilligan, C. A. (2008). Optimal observation times in experimental epidemic processes. Biometrics 64, 860-868.

Deardon, R., Brooks, S. P., Grenfell, B., Keeling, M. J., Tildesley, M., Savill, N., Shaw, D., & Woolhouse, M. (2010). Inference for individual-level models of infectious diseases in large populations. Statistica Sinica, 20(1), 239-261.

De Jong, M., & Kimman, T. G. (1994). Experimental quantification of vaccine-induced reduction in virus transmission. Vaccine, 12, 761-766.

Dewulf, J., Laevens, H., Koenen, F., Mintiens, K., & de Kruif, A. (2001). An experimental infection with classical swine fever virus in pregnant sows: transmission of the virus, course of the disease, antibody response and effect on gestation. Journal of veterinary medicine. B. 48, 583-591

Madden, L.V., Hughes, G., & van den Bosch, F. (2007). The Study of Plant Disease Epidemics. The American Phytopathological Society. St. Paul, MN: APS Press

Public Safety Canada. (2006). The United Kingdom Foot and Mouth Disease Crisis – Impact on Critical Infrastructure. Incident analysis IA06-001. Retrieved from http://www.publicsafety.gc.ca/prg/em/ccirc/2006/ia06-001-eng.aspx

Ritx, C., & Streibig, J. C. (2008). Nonlinear Regression With R. New York, NY: Springer Science + Business Media.

Seber, G. A. F., & Wild, C. J. (1989). Nonlinear regression. Hoboken, NJ: John Wiley and Sons, Inc..

Van Maanen, A., & Xu, X. M. (2003). Modeling plant disease epidemics. European Journal of Plant Pathology, 109(7), 669-682

Velthuis, A. G. J., Bouma, A., Katsma, W. E. A., Nodelijk G., & De Jong M. C. M. (2007). Design and analysis of small-scale transmission experiments with animals. Epidemiology and Infection, 135, 202-217

World Health Organization(WHO). (2010). Pandemic (H1N1) 2009 - update 100. Retrieved December 10, 2012, from http://www.who.int/csr/don/2010_05_14/en/index.html

World Health Organization(WHO). (2012, October 15). Smallpox. WHO Factsheet. Retrieved October 15, 2012, from http://www.who.int/csr/disease/smallpox/en/index.html

Appendix A

Results for Study 1

Table A.1: Model 1, Study 1

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,2,3,4 ,..., 20)	0.2602	2.9124	2.2024	0.6887
	(0.4204)	(0.599)	(0.4395)	(0.1081)
(2,4,6,8,...,20)	0.3631	3.2158	2.2275	0.8395
	(0.5616)	(0.6486)	(0.4479)	(0.129)
(3,6,9,...,18)	0.4571	3.6864	2.2004	1.0617
	(0.6608)	(0.716)	(0.4204)	(0.1789)
(4,8,12,...,20)	0.4703	5.4189	2.4312	1.9523
	(0.7094)	(1.0422)	(0.4773)	(0.3297)
(5,10,15,20)	0.4864	9.8961	2.3846	5.7164
	(0.7705)	(1.7679)	(0.478)	(0.9539)
(6,12,18)	0.5983	17.6446	2.2292	13.5627
	(1.1988)	(2.8578)	(0.4379)	(2.0559)
(10,20)	37121.38	1637.4961	3.0779	1672.1479
	(274153.5)	(237.9812)	(0.6876)	(243.2923)

Table A.2: Model 1, Study 1, Designs start at t=1 and 2

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,3,...,17,19)	0.3791	2.735	2.1969	0.5967
	(0.6405)	(0.5654)	(0.4318)	(0.0964)
(1,4,...,16,19)	0.4653	2.5456	2.1649	0.5561
	(0.8278)	(0.5263)	(0.432)	(0.0911)
(1,5,9,13,19)	0.5585	2.5393	2.1428	0.6226
	(0.9573)	(0.5165)	(0.4132)	(0.1007)
(1,6,11,16)	0.7484	2.4605	2.0881	0.7758
	(2.5623)	(0.4618)	(0.4072)	(0.1054)
(1,7,13,19)	0.8739	3.7305	3.4971	0.7342
	(3.7635)	(0.5167)	(0.4668)	(0.0826)
(2,4,6,...,18,20)	0.3631	3.2158	2.2275	0.8395
	(0.5616)	(0.6486)	(0.4479)	(0.129)
(2,5,...,17,20)	0.4547	2.9474	2.2823	0.6856
	(0.7768)	(0.6285)	(0.4718)	(0.1081)
(2,6,10,14,18)	0.5847	2.4046	2.0943	0.5946
	(1.1314)	(0.5009)	(0.4288)	(0.0852)
(2,7,12,17)	0.7388	2.6403	2.5177	0.4819
	(2.3571)	(0.4488)	(0.4531)	(0.061)
(2,8,14,20)	1.0055	2.6126	3.1745	0.3609
	(3.2664)	(0.4933)	(0.5326)	(0.0466)

Table A.3: Model 1, Study 1, Designs start at t=3 and 4

time points	$se(\theta_4)$	d_1	d_2	d_3
(3,5,7,...,19)	0.3523	4.6326	2.282	1.6481
	(0.5115)	(0.9178)	(0.453)	(0.2762)
(3,6, 9,...,18)	0.4571	3.6864	2.2004	1.0617
	(0.6608)	(0.716)	(0.4204)	(0.1789)
(3,7,11,15,19)	0.5375	3.2645	2.3398	0.6942
	(1.0373)	(0.6847)	(0.4612)	(0.1308)
(3,8,13,18)	0.6712	2.9395	2.5529	0.3914
	(1.1272)	(0.5448)	(0.4358)	(0.0844)
(4,6,8,...,20)	0.3327	8.0693	2.2856	4.3164
	(0.4881)	(1.394)	(0.4646)	(0.6188)
(4,7,10,13,16,19)	0.4155	6.2289	2.3004	2.8233
	(0.6174)	(1.1392)	(0.4629)	(0.4341)
(4,8,12,16,20)	0.4703	5.4188	2.4312	1.9523
	(0.7094)	(1.0421)	(0.4773)	(0.3297)
(4,9,14,19)	0.5538	4.6082	2.4252	1.3484
	(0.7886)	(0.9624)	(0.513)	(0.2753)
(4,10,16)	0.728	3.5316	2.1499	0.907
	(4.1828)	(0.7287)	(0.4367)	(0.2057)

Table A.4: Model 1, Study 1, Designs start at t=5 and 6

time points	$se(\theta_4)$	d_1	d_2	d_3
(5,7,...,17,19)	0.3617	14.8962	2.2523	10.6913
	(0.6106)	(2.2765)	(0.4663)	(1.4472)
(5,8,...,17,20)	0.4081	12.8967	2.3562	8.514
	(0.6676)	(2.1148)	(0.4968)	(1.2257)
(5,9,13,17)	0.4956	9.2826	2.2311	5.6932
	(0.7737)	(1.6457)	(0.4689)	(0.8816)
(5,10,15,20)	0.4864	9.896	2.3846	5.7164
	(0.7705)	(1.7679)	(0.478)	(0.9539)
(5,11,17)	0.561	7.8765	2.3685	4.2708
	(0.9549)	(1.5774)	(0.4778)	(0.7589)
(6,8,...,18,20)	0.4605	30.0143	2.2065	25.7436
	(1.1902)	(4.264)	(0.464)	(3.3439)
(6,9,12,15,18)	0.5251	22.5541	2.159	18.5992
	(1.122)	(3.2975)	(0.4351)	(2.5309)
(6,10,14,18)	0.5548	20.0505	2.1728	16.1496
	(1.1296)	(3.0603)	(0.4559)	(2.3042)
(6,11,16)	0.6172	16.5352	2.2066	12.9124
	(1.2106)	(2.5472)	(0.4335)	(1.8211)

Table A.5: Model 2, Study 1

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,2,3,...,20)	0.2794	0.6016	1.7439	2.1108	0.506
	(0.5821)	(1.0784)	(0.3565)	(0.3209)	(0.0849)
(2,4,6,8,...,20)	0.3965	0.8543	1.7704	2.0839	0.5441
	(0.8119)	(1.6125)	(0.3725)	(0.3292)	(0.0907)
(3,6,9,...,18)	0.5256	1.1929	1.9217	2.1834	0.554
	(1.09)	(2.4683)	(0.4426)	(0.3378)	(0.0945)
(4,8,12,...,20)	0.537	1.2422	2.4171	2.1244	0.8479
	(1.0839)	(3.246)	(0.6032)	(0.3804)	(0.175)
(5,10,15,20)	0.5534	1.5821	4.183	1.9282	2.694
	(1.1404)	(4.5608)	(0.9965)	(0.3758)	(0.5182)
(6,12,18)	0.6495	2.5347	9.0136	1.896	7.8144
	(1.3526)	(9.179)	(1.6852)	(0.3483)	(1.2798)

Table A.6: Model 2, Study 1, Designs start at t=1 and 2

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,3,...,17,19)	0.4041	0.869	1.7554	2.1545	0.4841
	(0.8692)	(1.4954)	(0.3508)	(0.3166)	(0.0823)
(1,4,7,...,16,19)	0.4886	1.0306	1.7008	2.1205	0.4797
	(1.0616)	(1.7973)	(0.3171)	(0.3061)	(0.0843)
(1,5,9,13,19)	0.617	1.3272	1.6974	2.0915	0.5761
	(1.4601)	(2.0113)	(0.3465)	(0.312)	(0.0948)
(1,6,11,16)	0.6723	1.5287	2.0888	3.0238	0.6371
	(1.8507)	(2.5645)	(0.3143)	(0.3889)	(0.0867)
(1,7,13,19)	0.729	1.245	2.3728	3.9195	0.57
	(2.3188)	(2.6459)	(0.3445)	(0.3384)	(0.0719)
(1,8,15)	2.2261	1.5724	1.3019	2.7073	0.6236
	(23.143)	(3.1899)	(0.2291)	(0.2505)	(0.1051)
(2,4,...,18,20)	0.3965	0.8543	1.7704	2.0838	0.5441
	(0.8119)	(1.6126)	(0.3725)	(0.3292)	(0.0907)
(2,5,...,17,20)	0.4833	1.0065	1.7576	2.1125	0.5189
	(1.019)	(1.847)	(0.3626)	(0.3357)	(0.086)
(2,6,10,14,18)	0.6111	1.267	1.6033	2.0807	0.5134
	(1.4211)	(2.0869)	(0.2836)	(0.309)	(0.0771)
(2,7,12,17)	0.6927	1.3436	2.2023	3.3699	0.4273
	(1.7411)	(2.5527)	(0.322)	(0.3365)	(0.0631)
(2,8,14,20)	0.9679	1.1572	1.7201	2.8001	0.3518
	(3.0299)	(2.5974)	(0.3134)	(0.3457)	(0.0526)
(2,9,16)	2.7552	1.562	0.9981	1.5632	0.4095
	(16.8463)	(3.1425)	(0.2281)	(0.2431)	(0.0572)

Table A.7: Model 2, Study 1, Designs start at t=3 and 4

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(3,5,7,9,...,19)	0.4075	0.9529	1.9968	2.1263	0.7013
	(0.8425)	(1.9872)	(0.4999)	(0.3505)	(0.1247)
(3,6, 9,...,18)	0.5256	1.1929	1.9217	2.1834	0.554
	(1.09)	(2.4683)	(0.4426)	(0.3378)	(0.0945)
(3,7,11,15,19)	0.5693	1.1934	1.9531	2.3236	0.4271
	(1.2312)	(2.3894)	(0.3781)	(0.3359)	(0.0782)
(3,8,13,18)	0.7532	1.3161	2.0402	2.5003	0.305
	(1.6955)	(3.1687)	(0.3918)	(0.3391)	(0.0633)
(3,9,15)	1.4232	1.7648	1.7101	1.8408	0.2524
	(5.7431)	(4.3332)	(0.3878)	(0.3403)	(0.0526)
(4,6,8,...,20)	0.3813	0.9899	2.7522	2.0166	1.5221
	(0.7573)	(3.0081)	(0.7342)	(0.384)	(0.2655)
(4,7,11,13,16,19)	0.4878	1.2019	2.2876	2.0777	1.0423
	(1.0314)	(2.9645)	(0.5889)	(0.3605)	(0.2024)
(4,8,12,16,20)	0.537	1.2422	2.4172	2.1244	0.8479
	(1.0839)	(3.2462)	(0.6032)	(0.3804)	(0.175)
(4,9,14,19)	0.6618	1.4496	2.3733	2.0283	0.6837
	(1.4122)	(4.2805)	(0.6706)	(0.4218)	(0.1587)
(4,10,16)	0.8423	1.985	2.2306	1.8361	0.5835
	(2.1187)	(4.6919)	(0.5278)	(0.3626)	(0.1405)

Table A.8: Model 2, Study 1, Designs start at t=5 and 6

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(5,7,9,...,17,19)	0.3982	1.2301	4.8622	1.9709	3.773
	(0.7931)	(4.27)	(1.1207)	(0.3945)	(0.6496)
(5,8,11,14,17,20)	0.452	1.3403	4.829	2.0538	3.3384
	(0.9047)	(6.161)	(1.2379)	(0.442)	(0.6009)
(5,9,13,17)	0.5831	1.9542	3.8939	2.0964	2.4457
	(1.1729)	(7.9907)	(1.057)	(0.4277)	(0.4818)
(5,10,15,20)	0.5534	1.5821	4.183	1.9282	2.694
	(1.1404)	(4.5608)	(0.9965)	(0.3758)	(0.5182)
(5,11,17)	0.6755	2.2512	3.8796	1.997	2.3673
	(1.6787)	(5.9208)	(0.9361)	(0.3839)	(0.4833)
(6,8,10,...,18,20)	0.4565	1.3746	12.2341	1.9434	11.1353
	(1.032)	(6.0627)	(2.2019)	(0.411)	(1.7511)
(6,9,12,15,18)	0.5489	2.0217	9.3706	1.9416	8.3535
	(1.1097)	(9.0951)	(1.7359)	(0.3891)	(1.3508)
(6,10,14,18)	0.592	2.3409	9.1028	1.9816	7.9237
	(1.216)	(15.6557)	(1.8218)	(0.4237)	(1.3178)
(6,11,16)	0.6882	3.1762	7.8481	2.0066	6.8346
	(1.478)	(15.6486)	(1.6795)	(0.3779)	(1.2546)

Table A.9: Model 3, Study 1

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,2,3,...,20)	0.4272	0.0996	2.7604	2.2063	0.5033
	(0.6981)	(0.1751)	(0.5872)	(0.4473)	(0.0831)
(2,4,6,...,20)	0.6221	0.1455	2.7364	2.1988	0.5113
	(1.031)	(0.2677)	(0.5749)	(0.4474)	(0.0836)
(3,6,9,...,18)	0.7805	0.1761	2.7633	2.1533	0.5116
	(1.2791)	(0.2976)	(0.5696)	(0.4232)	(0.0853)
(4,8,12,...,20)	1.6572	0.4984	3.139	2.4113	0.5491
	(9.9775)	(3.4941)	(0.7416)	(0.49)	(0.0933)

Table A.10: Model 3, Study 1, Designs start at t=1 and 2

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,3,5,...,19)	0.6034	0.1405	2.799	2.219	0.5012
	(0.9918)	(0.2439)	(0.6035)	(0.4481)	(0.084)
(1,4,7,...,19)	0.7704	0.1948	2.7448	2.2089	0.5211
	(1.5543)	(0.5634)	(0.5819)	(0.4483)	(0.0861)
(1,5,9,13,17)	1.2908	0.3087	2.704	2.1859	0.4759
	(2.2237)	(0.569)	(0.6313)	(0.4535)	(0.0751)
(1,6,11,16)	1.3869	0.2749	2.5768	2.1835	0.4602
	(2.4186)	(0.4709)	(0.5073)	(0.4232)	(0.0751)
(1,7,13,19)	1.2463	0.2368	2.7381	2.2784	0.5454
	(2.5128)	(0.6085)	(0.4809)	(0.4743)	(0.0933)
(1,8,15)	1.3136	0.3564	2.6619	2.1855	0.6134
	(2.4661)	(2.3289)	(0.4206)	(0.455)	(0.0983)
(2,4,6,...,20)	0.6221	0.1455	2.7364	2.1988	0.5113
	(1.031)	(0.2677)	(0.575)	(0.4474)	(0.0836)
(2,5,8,...,20)	0.8161	0.1898	2.8373	2.2753	0.4965
	(1.4977)	(0.3599)	(0.6278)	(0.4705)	(0.0813)
(2,6,10,14,18)	0.9405	0.1942	2.607	2.1352	0.4934
	(2.0908)	(0.3946)	(0.5301)	(0.4387)	(0.0842)
(2,7,12,17)	0.9141	0.2027	2.6104	2.1781	0.5417
	(1.9637)	(0.571)	(0.4923)	(0.4587)	(0.0941)
(2,8,14,20)	1.3986	0.8268	2.9937	2.406	0.7225
	(21.8467)	(22.5028)	(0.5009)	(0.5278)	(0.1319)

Table A.11: Model 3, Study 1, Designs start at t=3 and 4

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(3,5,7,...,19)	0.6894	0.1602	2.8585	2.2301	0.5181
	(1.1117)	(0.2792)	(0.6476)	(0.4527)	(0.0881)
(3,6, 9,...,18)	0.7805	0.1761	2.7633	2.1533	0.5116
	(1.2791)	(0.2976)	(0.5696)	(0.4232)	(0.0853)
(3,7,11,15,19)	0.7973	0.2086	2.8995	2.2825	0.5419
	(1.6005)	(0.8387)	(0.5777)	(0.4552)	(0.0936)
(3,8,13,18)	1.2147	0.4549	2.8658	2.2538	0.5834
	(7.3602)	(4.0252)	(0.5422)	(0.4542)	(0.103)
(4,6,8,...,18,20)	0.8367	0.1968	2.934	2.207	0.5818
	(1.481)	(0.4815)	(0.744)	(0.454)	(0.0985)
(4,7,11,13,16,19)	1.0302	0.2677	2.8767	2.2201	0.5709
	(3.3302)	(1.2319)	(0.6973)	(0.4558)	(0.0943)
(4,8,12,16,20)	1.6572	0.4984	3.139	2.4113	0.5491
	(9.9778)	(3.4942)	(0.7416)	(0.49)	(0.0933)

Table A.12: Model 3, Study 1, Designs start at t=5 and 6

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(5,7,9,...,17,19)	1.6211	0.3682	3.3129	2.2362	0.695
	(6.557)	(1.7102)	(1.1424)	(0.4603)	(0.2147)
(5,8,11,...,20)	3.1303	0.7592	3.5109	2.3578	0.6682
	(29.9686)	(7.5665)	(1.2573)	(0.5066)	(0.2242)
(6,8,10,...,20)	4.7595	0.9358	3.311	2.2587	0.6861
	(31.7391)	(6.4047)	(1.1068)	(0.4731)	(0.2155)

Table A.13: Model 4, Study 1

time points	d_1	d_2	d_3
(1,2,3,...,20)	2.3027	1.9923	0.4977
	(0.5255)	(0.4061)	(0.0826)
(2,4,6,8,..20)	2.3057	1.9921	0.5059
	(0.5243)	(0.4142)	(0.0833)
(3,6,9,...,18)	2.3639	1.9724	0.506
	(0.5262)	(0.3937)	(0.0845)
(4,8,12,...,20)	2.4572	2.0178	0.5872
	(0.6067)	(0.4015)	(0.0941)
(5,10,15,20)	2.5928	2.0249	0.5013
	(0.9823)	(0.3943)	(0.228)
(6,12,18)	2.7082	1.9383	0.4196
	(0.8352)	(0.3601)	(0.1932)

Table A.14: Model 4, Study 1, Designs start at t=1 and 2

time points	d_1	d_2	d_3
(1,3,5,...,17,19)	2.3104	1.997	0.4954
	(0.5238)	(0.3949)	(0.0835)
(1,4,7,...,16,19)	2.2184	1.9618	0.5137
	(0.499)	(0.3927)	(0.0859)
(1,5,9,13,19)	2.3178	2.0402	0.476
	(0.573)	(0.4166)	(0.0751)
(1,6,11,16)	2.1932	2.0509	0.4522
	(0.4482)	(0.3872)	(0.0739)
(1,7,13,19)	2.1374	2.0013	0.4881
	(0.3903)	(0.3989)	(0.0807)
(1,8,15)	2.3367	2.3295	0.5554
	(0.4146)	(0.4902)	(0.0837)
(2,4,6,...,18,20)	2.3057	1.9921	0.5059
	(0.5243)	(0.4142)	(0.0833)
(2,5,8,...,20)	2.3925	2.0687	0.4919
	(0.5817)	(0.4403)	(0.0806)
(2,6,10,14,18)	2.2498	2.0026	0.4851
	(0.5102)	(0.4291)	(0.0826)
(2,7,12,17)	2.1453	1.9694	0.5142
	(0.4105)	(0.395)	(0.089)
(2,8,14,20)	2.4229	2.1267	0.7895
	(0.4311)	(0.4813)	(0.185)
(2,9,16)	3.0605	2.0599	1.8524
	(0.5189)	(0.4503)	(0.3432)

Table A.15: Model 4, Study 1, Designs start at t=3 and 4

time points	d_1	d_2	d_3
(3,5,7,...,19)	2.3623	1.992	0.5141
	(0.5527)	(0.3893)	(0.0878)
(3,6, 9,...,18)	2.3639	1.9724	0.506
	(0.5262)	(0.3937)	(0.0845)
(3,7,11,15,19)	2.32	2.0037	0.5196
	(0.4727)	(0.3837)	(0.0908)
(3,8,13,18)	2.3155	1.9931	0.6437
	(0.4697)	(0.398)	(0.1227)
(3,9,15)	2.6492	2.0272	1.1213
	(0.5129)	(0.421)	(0.1913)
(4,6,8,...,18,20)	2.514	1.9989	0.5829
	(0.6852)	(0.4132)	(0.0996)
(4,7,10,...,19)	2.3412	1.9572	0.5683
	(0.5892)	(0.3847)	(0.0952)
(4,8,12,16,20)	2.4574	2.0178	0.5875
	(0.6067)	(0.4015)	(0.0942)
(4,9,14,19)	2.55	2.0938	0.6553
	(0.6879)	(0.4652)	(0.0931)
(4,10,16)	2.0103	1.8859	0.7592
	(0.5087)	(0.3603)	(0.0815)

Table A.16: Model 4, Study 1, Designs start at t=5 and 6

time points	d_1	d_2	d_3
(5,7,9,...,17,19)	2.8922	1.9998	0.7546
	(1.0534)	(0.3852)	(0.248)
(5,8,11,...,20)	3.0178	2.0823	0.7106
	(1.156)	(0.4393)	(0.2324)
(5,9,13,17)	2.82	2.0226	0.6341
	(1.1888)	(0.4017)	(0.2942)
(5,10,15,20)	2.5901	2.0249	0.4995
	(0.9824)	(0.3943)	(0.228)
(5,11,17)	2.6823	2.0222	0.5506
	(1.0691)	(0.3573)	(0.2932)
(6,8,10,...,20)	3.0965	2.0231	0.8819
	(1.0394)	(0.4191)	(0.2774)
(6,9,12,15,18)	3.1674	1.989	0.9194
	(1.116)	(0.3915)	(0.3533)
(6,10,14,18)	3.2424	2.016	0.7579
	(1.2816)	(0.4317)	(0.3266)
(6,11,16)	3.7714	2.0301	0.9776
	(1.5141)	(0.3676)	(0.544)

Appendix B

Results for Study 2

Table B.1: Model 1, Study 2

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,2,3,...,20)	0.1333 (0.156)	0.2942 (0.0516)	0.5839 (0.097)	0.256 (0.0319)
(2,4,6,...,20)	0.1882 (0.2302)	0.2989 (0.047)	0.5866 (0.0953)	0.2635 (0.0328)
(3,6,9,...,18)	0.2725 (0.3398)	0.2895 (0.05)	0.5812 (0.0905)	0.2441 (0.0333)
(4,8,12,...,20)	0.2346 (0.4155)	0.3735 (0.0498)	0.5539 (0.0918)	0.4438 (0.0737)
(5,10,15,20)	0.2324 (0.3556)	1.3705 (0.2603)	0.6022 (0.1075)	2.4412 (0.4337)
(6,12,18)	0.6225 (3.122)	8.6656 (1.3845)	0.7006 (0.1215)	11.9383 (1.9319)

Table B.2: Model 1, Study 2, Designs start at t=1 and 2

time points	$se(\theta_4)$	d_1	d_2	d_3
(1,3,5,...,19)	0.1922	0.2993	0.5864	0.2552
	(0.2321)	(0.0588)	(0.1001)	(0.0325)
(1,4,7,...,16,19)	0.2255	0.3124	0.5583	0.2528
	(0.3223)	(0.048)	(0.0918)	(0.0359)
(1,5,9,13,19)	0.2498	0.3308	0.8179	0.4501
	(0.4056)	(0.0564)	(0.1283)	(0.0529)
(1,6,11,16)	0.7574	0.1703	0.5828	0.64
	(4.7931)	(0.0265)	(0.0688)	(0.0697)
(1,7,13,19)	2.2351	0.3593	0.1168	0.3238
	(20.6838)	(0.0688)	(0.0459)	(0.0701)
(2,4,6,...,18,20)	0.1882	0.2989	0.5866	0.2635
	(0.2302)	(0.047)	(0.0953)	(0.0328)
(2,5,8,...,20)	0.2239	0.3334	0.6501	0.3015
	(0.2877)	(0.061)	(0.1122)	(0.0368)
(2,6,10,14,18)	0.4458	0.1826	0.5884	0.3535
	(1.4692)	(0.0332)	(0.0734)	(0.0373)
(2,7,12,17)	1.3829	0.336	0.236	0.3398
	(10.1013)	(0.0535)	(0.0513)	(0.0354)
(2,8,14,20)	1.0592	0.4875	0.3174	0.0829
	(6.5212)	(0.0849)	(0.0616)	(0.0128)
(2,9,16)	0.6138	0.6522	0.4596	0.0813
	(2.6108)	(0.1306)	(0.0816)	(0.0109)

Table B.3: Model 1, Study 2, Designs start at t=3 and 4

time points	$se(\theta_4)$	d_1	d_2	d_3
(3,5,7,...,19)	0.1966	0.3132	0.5718	0.3356
	(0.2275)	(0.061)	(0.0982)	(0.0461)
(3,6, 9,...,18)	0.2725	0.2895	0.5812	0.2441
	(0.3398)	(0.05)	(0.0905)	(0.0333)
(3,7,11,15,19)	0.4002	0.2853	0.432	0.1478
	(1.0054)	(0.0649)	(0.084)	(0.0239)
(3,8,13,18)	0.4048	0.4043	0.4724	0.0873
	(1.1307)	(0.0836)	(0.0898)	(0.0186)
(3,9,15)	0.3645	0.5855	0.4932	0.1182
	(0.8879)	(0.1041)	(0.0893)	(0.0245)
(4,6,8,...,20)	0.1804	0.424	0.5578	0.7204
	(0.2265)	(0.0584)	(0.0915)	(0.102)
(4,7,10,13,16,19)	0.2247	0.3706	0.5528	0.5134
	(0.3344)	(0.0504)	(0.09)	(0.0837)
(4,8,12,16,20)	0.2346	0.3735	0.5539	0.4438
	(0.4155)	(0.0498)	(0.0918)	(0.0737)
(4,9,14,19)	0.241	0.405	0.5625	0.4267
	(0.4764)	(0.054)	(0.0921)	(0.0744)
(4,10,16)	0.261	0.436	0.5608	0.4277
	(0.4886)	(0.0619)	(0.0944)	(0.0745)

Table B.4: Model 1, Study 2, Designs start at t=5 and 6

time points	$se(\theta_4)$	d_1	d_2	d_3
(5,7,9,...,17,19)	0.208	1.762	0.5801	2.952
	(0.3352)	(0.3209)	(0.1005)	(0.4771)
(5,8,11,...,20)	0.2169	1.5262	0.5862	2.5866
	(0.3387)	(0.2819)	(0.1034)	(0.4192)
(5,9,13,17)	0.2495	1.369	0.5936	2.4495
	(0.3841)	(0.2495)	(0.1059)	(0.4036)
(5,10,15,20)	0.2324	1.3705	0.6022	2.4412
	(0.3556)	(0.2603)	(0.1075)	(0.4337)
(5,11,17)	0.2646	1.7296	0.6001	2.6973
	(0.3997)	(0.364)	(0.106)	(0.4937)
(6,8,10,...,20)	0.6873	8.669	0.6625	12.0342
	(10.772)	(1.4542)	(0.1203)	(1.9638)
(6,9,12,15,18)	0.595	7.6853	0.6786	10.9272
	(4.0924)	(1.2149)	(0.1222)	(1.6634)
(6,10,14,18)	0.5838	7.0993	0.6682	10.1515
	(3.4208)	(1.0731)	(0.1188)	(1.4869)
(6,11,16)	0.6715	8.2173	0.6697	11.398
	(4.0517)	(1.5103)	(0.1158)	(2.0556)

Table B.5: Model 2, Study 2

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,2,3,...,20)	0.1334	0.255	0.3012	0.6269	0.2427
	(0.1551)	(0.3303)	(0.0538)	(0.1016)	(0.0307)
(2,4,6,...,20)	0.1889	0.3562	0.3048	0.628	0.2489
	(0.231)	(0.4868)	(0.0493)	(0.0998)	(0.0315)
(3,6,9,...,18)	0.2728	0.4857	0.2928	0.6212	0.2289
	(0.34)	(0.6713)	(0.0525)	(0.0946)	(0.0315)
(4,8,12,...,20)	0.2412	0.4977	0.3708	0.5866	0.4125
	(0.4233)	(0.8449)	(0.0511)	(0.0957)	(0.0686)
(5,10,15,20)	0.2469	0.5655	1.233	0.6143	2.2843
	(0.3915)	(0.8981)	(0.2458)	(0.1083)	(0.426)
(6,12,18)	0.6785	0.7698	8.5154	0.7016	11.9983
	(3.273)	(1.308)	(1.5441)	(0.1256)	(2.1728)

Table B.6: Model 2, Study 2, Designs start at t=1 and 2

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(1,3,5,...,17,19)	0.1925	0.3723	0.3073	0.6316	0.2431
	(0.23)	(0.4821)	(0.0609)	(0.1048)	(0.0314)
(1,4,7,...,16,19)	0.2277	0.438	0.3234	0.5994	0.2417
	(0.3261)	(0.6472)	(0.0506)	(0.0966)	(0.0347)
(1,5,9,13,19)	0.2495	0.556	0.3185	0.8661	0.4009
	(0.3575)	(0.8246)	(0.0556)	(0.1284)	(0.0471)
(1,6,11,16)	0.5451	0.5631	0.1404	0.5919	0.4889
	(2.182)	(0.9002)	(0.0252)	(0.0711)	(0.0519)
(1,7,13,19)	1.9232	0.4732	0.4622	0.1829	0.6092
	(13.1122)	(0.9004)	(0.0669)	(0.0393)	(0.0606)
(1,8,15)	2.1467	0.6658	0.5849	0.2192	0.2046
	(9.8763)	(1.5727)	(0.0919)	(0.0389)	(0.0201)
(2,4,6,...,18,20)	0.1889	0.3562	0.3048	0.628	0.2489
	(0.231)	(0.4868)	(0.0493)	(0.0998)	(0.0315)
(2,5,8,...,17,20)	0.2245	0.424	0.3361	0.6968	0.287
	(0.2819)	(0.5597)	(0.062)	(0.1167)	(0.0355)
(2,6,10,14,18)	0.3908	0.4839	0.1919	0.5993	0.3041
	(0.9571)	(0.6826)	(0.0363)	(0.0765)	(0.0324)
(2,7,12,17)	0.8313	0.5523	0.2686	0.2827	0.2193
	(3.2064)	(0.87)	(0.0482)	(0.0594)	(0.0209)
(2,8,14,20)	0.7396	0.4751	0.4449	0.375	0.0412
	(2.7622)	(0.8821)	(0.0882)	(0.0782)	(0.0062)
(2,9,16)	0.5277	0.6181	0.95	0.6088	0.1261
	(1.8551)	(1.4429)	(0.1739)	(0.1152)	(0.0156)

Table B.7: Model 2, Study 2, Designs start at t=3 and 4

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(3,5,7,...,19)	0.1984	0.3895	0.3084	0.6133	0.306
	(0.2304)	(0.52)	(0.0606)	(0.1026)	(0.0421)
(3,6, 9,...,18)	0.2728	0.4857	0.2928	0.6212	0.2289
	(0.34)	(0.6713)	(0.0525)	(0.0946)	(0.0315)
(3,7,11,15,19)	0.38	0.4981	0.3075	0.4724	0.1412
	(0.8244)	(0.719)	(0.0698)	(0.0901)	(0.0233)
(3,8,13,18)	0.3865	0.5794	0.4605	0.5382	0.0887
	(0.9434)	(0.9413)	(0.0934)	(0.1004)	(0.0186)
(3,9,15)	0.3668	0.7642	0.7348	0.602	0.1272
	(0.8335)	(1.4972)	(0.1172)	(0.1024)	(0.0266)
(4,6,8,...,18,20)	0.1841	0.3598	0.3609	0.586	0.6084
	(0.2362)	(0.5524)	(0.0504)	(0.0947)	(0.0865)
(4,7,10,...,19)	0.2307	0.4651	0.3467	0.5821	0.4552
	(0.3484)	(0.7478)	(0.049)	(0.0934)	(0.0747)
(4,8,12,16,20)	0.2412	0.4977	0.3708	0.5866	0.4125
	(0.4233)	(0.8449)	(0.0511)	(0.0957)	(0.0686)
(4,9,14,19)	0.2508	0.5884	0.4131	0.6026	0.4055
	(0.49)	(1.0913)	(0.0569)	(0.0957)	(0.0704)
(4,10,16)	0.2774	0.8256	0.4452	0.617	0.4052
	(0.518)	(1.5196)	(0.0658)	(0.0996)	(0.07)

Table B.8: Model 2, Study 2, Designs start at t=5 and 6

time points	$se(\theta_4)$	$se(\theta_5)$	d_1	d_2	d_3
(5,7,9,...,17,19)	0.2121	0.3682	1.4161	0.588	2.4929
	(0.3484)	(0.6468)	(0.2856)	(0.101)	(0.4388)
(5,8,11,...,20)	0.2241	0.4204	1.3021	0.5965	2.2977
	(0.3537)	(0.7269)	(0.2484)	(0.1044)	(0.3854)
(5,9,13,17)	0.2646	0.6347	1.1925	0.6111	2.2126
	(0.4199)	(1.116)	(0.2308)	(0.1073)	(0.3889)
(5,10,15,20)	0.2469	0.5655	1.233	0.6143	2.2843
	(0.3915)	(0.8981)	(0.2458)	(0.1083)	(0.426)
(5,11,17)	0.2883	0.8429	1.5767	0.617	2.5298
	(0.4463)	(1.3302)	(0.347)	(0.1074)	(0.4831)
(6,8,10,...,18,20)	0.4914	0.3088	6.9385	0.6539	9.93
	(2.4405)	(0.6545)	(1.0657)	(0.1195)	(1.4393)
(6,9,12,15,18)	0.5556	0.4645	6.4873	0.6726	9.4757
	(2.6622)	(0.988)	(1.0245)	(0.1212)	(1.4109)
(6,10,14,18)	0.5875	0.5459	6.3667	0.6655	9.2854
	(2.8596)	(1.0713)	(1.0248)	(0.1183)	(1.4182)
(6,11,16)	0.6923	0.821	7.329	0.6653	10.3453
	(3.3436)	(1.6242)	(1.228)	(0.1144)	(1.6842)

Table B.9: Model 3, Study 2

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,2,3,4,...,20)	0.2647	0.0746	0.2906	0.5674	0.2329
	(0.3399)	(0.0972)	(0.0513)	(0.0949)	(0.0298)
(2,4,6,8,..,20)	0.4023	0.1153	0.2983	0.5748	0.2245
	(0.5913)	(0.1813)	(0.0475)	(0.0939)	(0.0291)
(3,6,9,...,18)	0.8703	0.3609	0.2883	0.5774	0.3231
	(15.421)	(7.8034)	(0.0502)	(0.0965)	(0.0399)

Table B.10: Model 3, Study 2, Designs start at t=1 and 2

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(1,3,5,...,17,19)	0.3649	0.1026	0.2944	0.5656	0.2499
	(0.4769)	(0.143)	(0.0587)	(0.0973)	(0.0328)
(1,4,7,...,16,19)	0.6564	0.2033	0.3109	0.5708	0.2055
	(1.1545)	(0.3846)	(0.0489)	(0.0911)	(0.0283)
(1,5,9,13,19)	0.6839	0.1678	0.2903	0.5835	0.2818
	(1.0832)	(0.26)	(0.0548)	(0.1035)	(0.0399)
(1,6,11,16)	0.6942	0.1741	0.3377	0.5958	0.4843
	(1.0952)	(0.4752)	(0.0526)	(0.1024)	(0.0576)
(2,4,6,...,18,20)	0.4023	0.1153	0.2983	0.5748	0.2245
	(0.5913)	(0.1813)	(0.0475)	(0.0939)	(0.0291)
(2,5,8,...,17,20)	0.4409	0.1122	0.3106	0.5753	0.2706
	(0.7466)	(0.1711)	(0.0601)	(0.1006)	(0.038)
(2,6,10,14,18)	0.4858	0.1783	0.3228	0.609	0.4341
	(1.1081)	(1.2592)	(0.0519)	(0.1012)	(0.0558)

Table B.11: Model 3, Study 2, Designs start at t=3 and 4

time points	$se(\theta_4)$	$se(\theta_6)$	d_1	d_2	d_3
(3,5,7,9,...,19)	0.4188	0.1178	0.299	0.5678	0.2505
	(0.5476)	(0.1684)	(0.0593)	(0.0979)	(0.0334)
(3,6, 9,...,18)	0.8703	0.3609	0.2883	0.5774	0.3231
	(15.42)	(7.8029)	(0.0502)	(0.0965)	(0.0399)
(4,6,8,...,18,20)	1.1505	0.361	0.3228	0.5869	0.1793
	(13.3381)	(4.4834)	(0.0493)	(0.0957)	(0.025)

Table B.12: Model 4, Study 2

time points	d_1	d_2	d_3
(1,2,3,4,...,20)	0.2911	0.5754	0.231
	(0.0518)	(0.0957)	(0.0297)
(2,4,6,8,...,20)	0.2981	0.5823	0.2231
	(0.0479)	(0.0948)	(0.029)
(3,6,9,...,18)	0.2909	0.5849	0.311
	(0.0507)	(0.0974)	(0.0378)
(4,8,12,...,20)	0.3194	0.5694	0.1365
	(0.0482)	(0.092)	(0.0122)
(5,10,15,20)	0.863	0.6073	0.0741
	(0.139)	(0.1076)	(0.0107)
(6,12,18)	1.3276	0.6998	0.2908
	(0.1828)	(0.1212)	(0.0346)

Table B.13: Model 4, Study 2, Designs start at t=1 and 2

time points	d_1	d_2	d_3
(1,3,5,...,17,19)	0.2959	0.574	0.2473
	(0.0593)	(0.0981)	(0.0325)
(1,4,7,...,19)	0.3123	0.5789	0.2057
	(0.0494)	(0.0918)	(0.0283)
(1,5,9,13,19)	0.2923	0.5941	0.2784
	(0.0555)	(0.1047)	(0.0392)
(1,6,11,16)	0.3365	0.6215	0.4998
	(0.0539)	(0.1034)	(0.0612)
(2,4,6,...,18,20)	0.2981	0.5823	0.2231
	(0.0479)	(0.0948)	(0.029)
(2,5,8,...,17,20)	0.3104	0.5816	0.267
	(0.0606)	(0.1012)	(0.0373)
(2,6,10,14,18)	0.3223	0.6136	0.4156
	(0.0532)	(0.1018)	(0.0511)
(2,7,12,17)	0.7147	0.603	1.1284
	(0.1239)	(0.0965)	(0.1747)
(2,8,14,20)	1.1363	0.5784	2.0777
	(0.1755)	(0.0956)	(0.1607)
(2,9,16)	1.076	0.5706	2.1625
	(0.133)	(0.0891)	(0.0937)

Table B.14: Model 4, Study 2, Designs start at t=3 and 4

time points	d_1	d_2	d_3
(3,5,7,...,19)	0.2998	0.5753	0.2481
	(0.0598)	(0.0986)	(0.0332)
(3,6, 9,...,18)	0.2909	0.5849	0.311
	(0.0507)	(0.0974)	(0.0378)
(3,7,11,15,19)	0.3758	0.5641	0.5287
	(0.0677)	(0.0938)	(0.067)
(3,8,13,18)	0.4496	0.543	0.8324
	(0.0841)	(0.0919)	(0.0603)
(3,9,15)	0.4221	0.5251	0.8601
	(0.0689)	(0.0857)	(0.0406)
(4,6,8,...,20)	0.3203	0.5905	0.1835
	(0.0494)	(0.096)	(0.0257)
(4,7,10,...,,19)	0.3367	0.584	0.1485
	(0.0497)	(0.0927)	(0.0197)
(4,8,12,16,20)	0.3194	0.5694	0.1366
	(0.0482)	(0.092)	(0.0122)
(4,9,14,19)	0.2895	0.5631	0.1345
	(0.0477)	(0.0904)	(0.0112)
(4,10,16)	0.2918	0.5682	0.1392
	(0.0508)	(0.0938)	(0.0131)

Table B.15: Model 4, Study 2, Designs start at t=5 and 6

time points	d_1	d_2	d_3
(5,7,9,...,17,19)	0.7481	0.6119	0.1478
	(0.1298)	(0.1058)	(0.0242)
(5,8,...,17,20)	0.9665	0.605	0.1327
	(0.1533)	(0.1063)	(0.0123)
(5,9,13,17)	0.9209	0.6069	0.1142
	(0.1438)	(0.1072)	(0.0146)
(5,10,15,20)	0.861	0.6073	0.0735
	(0.1383)	(0.1076)	(0.0107)
(5,11,17)	0.7422	0.6098	0.0603
	(0.1251)	(0.1066)	(0.01)
(6,8,10,...,18,20)	2.7408	0.668	1.1354
	(0.3475)	(0.1219)	(0.09)
(6,9,12,15,18)	2.6357	0.6802	1.081
	(0.2802)	(0.1227)	(0.0975)
(6,10,14,18)	2.2454	0.6686	0.7206
	(0.2412)	(0.1191)	(0.0502)
(6,11,16)	1.7112	0.6669	0.4535
	(0.2052)	(0.1148)	(0.0439)