A stochastic model for the assessment of the transmission pathways of heart and skeleton muscle inflammation, pancreas disease and infectious salmon anaemia in marine fish farms in Norway

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Abstract

Salmon farming is threatened, economically and ecologically, by infectious diseases. To reduce the risk of epidemics, authorities have developed regulations. These are based on quantitative understanding of pathways of infection, representing disease specific risks. A stochastic model was fitted to historical data, to estimate risk factors associated with competing spread mechanisms. Three infectious diseases were compared, heart and skeletal muscle inflammation (HSMI), pancreas disease (PD) and infectious salmon anaemia (ISA). This study was based on space-time data, from Norway from 2003 to 2007, describing the susceptible fish cohorts and the reported infections. Particular interest was given to seaway distances between farms and their local management organisation. The parameter measuring the effect of distance to an infectious fish farm was positive and significant for all diseases, implying that the risk involved with proximate infectious fish farms increased with decreasing distance. For HSMI and PD there was a significant effect of sharing a contact network with an infectious farm. For HSMI, but not for PD or ISA, there was a significant effect of previous infected cohorts on the same farm. The relative contribution of each transmission pathway was dominated by seaway distance for PD and HSMI, while other non-defined pathways dominated for ISA. This comparative study highlights that the three diseases have different patterns of spread, with important consequences for disease prevention and management.

KEY WORDS: Modeling; Infectious salmon anemia; Heart and skeletal muscle inflamation; Pancreas disease; Space-time data

1 Introduction

Infectious diseases are a constant threat to the fish farming industry with major economic implications, in addition to being a problem for fish welfare and the environment. In salmon farming, diseases with a viral aetiology are particularly hard to control since medical treatment and vaccines seem generally less effective than, for example, diseases with a bacteriological aetiology. The remaining control options are bio-security measurements aimed either to control the spread of viral infectious agents or to reduce the risk of disease outbreaks from infected fish. Therefore, insights into the transmission pathways of disease agents and risk factors for disease outbreaks are important.

The spread of infectious diseases, as a complex dynamical system with high level interaction, has an inherent element of randomness. Stochastic models are a useful tool for describing the dissemination of a disease between fish farms and for testing hypotheses on transmission pathways. Scheel et al. (2007) proposed a statistical model for the spread of infectious salmon anaemia (ISA) between fish farms. We now take this approach further and present the statistical model of Scheel et al. (2007) so that it can be applied to other infectious diseases, together with additional data, as well. We decompose the infection rate at a susceptible farm into four possible transmission pathways: i) transmission from adjacent infected farms, where the infection rate decreases by increasing seaway distance to an infected farm, ii) transmission from infected farms within shared local contact networks, iii) transmission from a previous infected fish cohort resident at the same farm, and iv) transmission via other pathways. The third component is new with respect to Scheel et al. (2007). Each infection rate may depend on characteristics of the fish populations at the susceptible and infectious fish farms. We present our model in a user-oriented fashion, adding a careful step-by-step guide on how to interprete inferential results.

The main focus of this paper is on comparing the transmission mechanisms of different infectious diseases. By applying our statistical model to three infectious diseases, we reveal important differences in the way these infections spread between fish farms, with implications for preventive policies.

Three important infectious diseases for Norwegian marine salmon farming are studied: heart and skeletal muscle inflammation (HSMI), pancreas disease (PD) and infectious salmon anaemia (ISA). HSMI is an infectious disease of Atlantic salmon (*Salmo salar* L.) with unknown aetiology, but where a viral aetiology is strongly suggested (Kongtorp et al. 2004a). PD is a disease of both Atlantic salmon and rainbow trout (*Oncorhynchus mykiss* Walbaum), caused by salmonid alpha virus, SAV (Weston et al. 2002). ISA is a disease of Atlantic salmon caused by the infectious salmon anaemia virus, ISAV (Falk et al. 1997). The present data set consist of monthly production data on all marine Atlantic salmon and rainbow

trout farms in Norway from February 2003 to the end of 2007, with the history of recorded outbreaks corresponding to the three diseases. The purpose of the present study is to compare the spatio-temporal dynamics of recorded outbreaks of the three diseases. Specifically, we compare the proportions of outbreaks that the statistical model assigns to the different transmission pathways. Furthermore, we compare the effects of different life histories of fish cohorts on infection rates. We also investigate how susceptibility and infectiousness depend on the of the size of a fish cohort.

2 Three infectious diseases

HSMI, PD and ISA are all economically important diseases in salmon farming, and they share the characteristic that disease outbreaks, with few exceptions, occur in the marine phase of the production. In Norway, HSMI and PD are considered to be emerging diseases with increasing numbers of outbreaks in the last years. The number of outbreaks of ISA has been lower and relatively stable over many years. This disease, however, has been subject to a stricter management regime due to an earlier history of excessive numbers of outbreaks (see Lyngstad et al. 2008).

2.1 Heart and skeletal muscle inflammation

Heart and skeletal muscle inflammation(HSMI) has only been recorded in Atlantic salmon and was diagnosed for the first time in the Trøndelag County in Mid-Norway in 1999. Between 2004 and 2007 the annual number of recorded outbreaks in Atlantic salmon farms has tripled. Mid-Norway remains the focal area for the disease, but new registrations occur all along the coast where salmon farming is practised.

HSMI is a transmissible disease, but the infectious agent has yet to be identified. Antibiotic treatment and filtration of tissue homogenate used to experimentally infect salmon, as well as findings of virus-like particles associated with the disease, all tend to suggest that the infectious agent is of viral nature (Kongtorp et al. 2004a; Watanabe et al. 2006). HSMI-diseased fish are typically anorexic and display abnormal swimming behaviour. Necropsy findings typically include a pale heart, yellow liver, ascites, swollen spleen and petechiae in the perivisceral fat (Kongtorp et al. 2004b). Diagnosis of HSMI is based on histological examination. Mortality associated with HSMI is usually reported to be low, but morbidity in the form of lesions in the heart and somatic muscle tissues appears in nearly all fish in affected farms (Kongtorp et al. 2006; Watanabe et al. 2006).

2.2 Pancreas disease

Pancreas disease (PD) is a disease recorded in both Atlantic salmon and rainbow trout in Norway. The causal viral agent, Norwegian salmonid alpha virus (SAV) , was first isolated from farmed Atlantic salmon in Norway in 1997 (Christie et al. 1998) and is now recognised as a subtype of SAV (McLoughlin and Graham 2007). PD outbreaks in Norway have increased markedly in the last few years. PD was initially confined to the Hordaland County, but the distribution of outbreaks has expanded and the main affected area now covers the whole West-Coast of Norway. Occasional outbreaks of PD have also been recorded in North Norway

(Kristoffersen et al. 2008).

Experimental evidence suggests that SAV is highly capable of horizontal transmission between cohabitant fish (Raynard and Houghton, 1993; McLoughlin et al., 1996). Phylogenetic and risk factor studies also strongly support horizontal spread of PD between salmon farms (Fringuelli et al., 2008; Kristoffersen et al., 2008). Mortality during PD outbreaks varies; from sub-clinical infections of PD with no associated mortality (Graham et al. 2006), to reports of up to 63% mortality during an outbreak (Crockford et al. 1999).

2.3 Infectious salmon anaemia

Infectious salmon anaemia (ISA) is a viral disease that predominantly affects Atlantic salmon, and was first diagnosed in Norway in 1984 (Thorud and Djupvik, 1984). The annual number of outbreaks of ISA in Norway peaked in 1990 with 80 recorded outbreaks, after which the Norwegian veterinary authorities implemented several regulations to control the disease (see Lyngstad et al. 2008). From 1993 to 2007 the annual number of outbreaks of ISA in Norway has varied between 1 and 23, widespread along the coast. ISA outbreaks have appeared partly isolated in space and time but partly also as small space-time clusters of outbreaks. This clustering, along with phylogenetic studies suggest that ISA is partly spread horizontally between fish farms (Gustafson et al. 2007; Scheel et al., 2007; Lyngstad et al., 2008).

3 Data

3.1 The study population

The Norwegian fish farming industry is organised such that any operator of a fish farming operation must have a legal concession authorised by the Directory of Fisheries (DFF; www.fiskeridir.no). Licenses to operate specific geo-referenced fish farms are legally authorised within the concessions. All authorised fish farms, and the concessions these are attached to, are registered in the aquaculture license register of DFF. The aquaculture license register provided geo-references for fish farms, as well as unique identities for fish farms and concessions, in the present study.

Every operator of a marine fish farm in Norway holding salmonids are required to report key production statistics to responsible authorities on a monthly basis. The present data include all Norwegian marine fish farms with a standing stock of Atlantic salmon or rainbow trout in any month from February 2003 to December 2007. This constitutes a total of 1082 fish farms, of which 1035 fish farms produced Atlantic salmon only. For each fish farm, the location and monthly figures of total biomass and the number of fish on farm are given.

Within the five year period of data, each fish farm had normally several (maximum 6) production periods, i.e. consecutive periods of production of fish populations, interrupted by periods of fallowing (no fish on farm). The fish population within a production period was termed a cohort and the present data consists of 2566 cohorts, with between one and six cohorts per fish farm.

Each cohort, except those that were removed in 2003, was classified into one of four categories; i) autumn-smolt cohorts (start weight smaller than 250g and the fish stocked in the period August-February), ii) spring-smolt cohorts (start weight smaller than 250g and the fish stocked in the period March-July), iii) mixed cohorts (fish are stocked several times during the production period) and relocated cohorts (start weight more than 250g and the fish were probably moved from an other marine fish farm). The cohorts were distributed as 20% autumn-smolt cohorts, 33% spring-smolt cohorts, 14% mixed cohorts and 33% relocated cohorts.

For every pair of fish farms, the seaway distance was calculated using the Arc View extension Spatial Analyst (ESRI, Redlands, CA, USA). The geographic coordinates were downloaded from the aquaculture licence register of DFF. Distances in excess of 100 km were truncated to 100 km. The various fish farms had between 0 and 23 other fish farms within a distance of 10 km (median 4).

Fish farms sharing a common concession identity in the aquaculture licence register were defined to constitute a local contact network. These had a common

ownership and were usually located in relative proximity, and such fish farms are often operated by the same staff or they may share equipment. There was 269 such contact networks. A fish farm shared contact network with between 0 and 15 other fish farms (median 4). The distances between pairs of fish farms within the same contact network varied between 0.2 and 99 km (median 13).

The production statistics used in the present study, as well as the seaway distances and contact networks, were the same as those used by Kristoffersen et al. (2008), and details on the treatment and compilation of the data are given by these authors.

3.2 Disease outbreak history

Disease notification on a fish farm at time t is termed a recorded outbreak of disease in the cohort of fish on the farm.

The data on recorded outbreaks of HSMI used in the present study were compiled from the Laboratory information system at the NVI. Clinical diagnoses of HSMI are based on clinical signs, i.e. fish mortality and abnormal swimming behaviour, along with histopathological examinations. Due to NVI's leading role as a diagnostic laboratory for HSMI, nearly all diagnoses of this disease are done by the NVI (Ruth Torill Kongtorp, personal communication). However, because HSMI is a relatively novel disease which is not notifiable, and symptoms may be confused with other disease syndromes (Kongtorp et al., 2004a and b), we expect that HSMI was underreported in the present data and perhaps especially so in the early study period. The recorded month of a HSMI outbreak corresponds to the month when a clinical diagnosis was recorded in the Laboratory information system on a given fish farm.

Data on recorded outbreaks of PD were compiled by the NVI and the Norwegian Food Safety Authority (NFSA). The present data on PD outbreaks have been analysed in an earlier study, but with a different aim, approach and method (see Kristoffersen et al. 2008). The recorded month of a PD outbreak corresponds to the month when a clinical diagnosis was recorded on a given fish farm.

Data on recorded outbreaks of ISA used in the present study were compiled from the Laboratory information system at the NVI, which acts as a national and international reference laboratory for ISA. Fish samples from all suspected outbreaks of ISA in Norway are analysed at the NVI. The recorded month of an ISA outbreak corresponds to the month when the first samples of fish were received at the NVI, and that shortly later resulted in a clinical diagnosis of ISA on a given fish farm.

In the data period there were 375 recorded outbreaks of HSMI, 225 of PD and 47 of ISA. For all disease outbreaks there were registered cohorts of fish (positive

biomass records) on given fish farms in the month of the recorded outbreaks, or in the previous two months. If the registered biomass was zero in the month of an outbreak record, but positive in one of the two previous months, the time of the outbreak was reassigned to the month with the last registered positive biomass. There were also a few recorded disease outbreaks (8 for HSMI, 2 for PD and 1 for ISA) for which there was no registered biomass on the given fish farms corresponding to the month of the outbreak record, or the two previous months. These outbreaks were ignored in the present analyses.

Of all pairs of two subsequent cohorts at the same fish farm where the first cohorts had an outbreak of HSMI, 52 % of the second cohorts also experienced an outbreak of HSMI. If the first cohorts did not experienced an outbreak, only 16 % of the second cohorts experienced an outbreak. For PD the corresponding proportions were 18 % and 11 %, and for ISA 0 % and 2 %, respectively. Of all cohorts with an outbreak of HSMI recorded from January 2004 and later, 16 % had a previous infectious fish cohort at the same farm i at most six months before the current fish cohort were stocked. For PD and ISA the corresponding numbers were 7 % and 0 %, respectively.

The majority of cohorts with outbreaks of HSMI or PD had at least one identified fish farm in the neighbourhood that was a potential source of infection, in that 91 % (HSMB) and 95 % (PD) of the outbreaks had a previous outbreak within the last year and within a distance of 50 km. However, most of the outbreaks of ISA were isolated: only 47 % of the outbreaks had previous outbreaks within a distance of 50 km.

4 Methods

The stochastic infectious disease model we present in this section is an extension of Scheel et al. (2007). It can be applied to different diseases and data sources. First we present the model, then describe how parameters are estimated, and finally outline how inferential results can be interpreted.

4.1 The transmission model

The point in time when a fish farm is infected is called event time. The key concept in our statistical model is the infection rate for a given susceptible fish farm at a given time t, which can be interpreted as the probability that the susceptible fish farm will become infected per time unit in a small interval around t. This is modelled for all fish farms in Norway simultaneously on a continuous time scale, even though the data are only available monthly.

For each disease outbreak, we know the time when the outbreak was recorded, but the actual event time of infection, anterior to the recording time, is unknown, and it is the latter that is modelled. There is always a time delay between infection and reporting, including at least the time it takes for the virus to spread locally within the fish farm into a visible outbreak, and perhaps also a shorter delay from outbreak detection to reporting. The time delay may vary from outbreak to outbreak, and even location-wise, but for simplicity we first assume that it is constant and common for all outbreaks. In principle the time delay is a parameter that could be estimated from the data. However, without additive data monitoring this delay, it is difficult to estimate it precisely. We propose two strategies. First, we fix the time delay and estimate the rest of the statistical model by conditioning on that fixed value. We make calculations for three different time delay values: 3, 6 or 9 months. In addition to calculations with a fixed, common delay, we assume that the delay of each specific infection event is random and draw the delay times from a uniform distribution between 3 and 9 months. This covers a reasonable span of what the true average time delay may be for the three diseases considered here; see for instance the discussion in Scheel et al. (2007) regarding ISA. The time from when a cohort is stocked until the registration of a disease outbreak in that particular cohort may sometimes be shorter than the fixed or random time delay. In such cases the event time is set to the time of the stocking of the given fish cohort.

We assume that a fish cohort and the fish farm it belongs to are susceptible to infection from the time a fish cohort is stocked until the cohort (and the fish farm) becomes infected or the cohort is removed from the fish farm. Further, we assume that an infected cohort and the corresponding fish farm is infectious from the time immediately after an infection event in the cohort and until the cohort

is removed. See Figure 1 for an illustration. However, since the data are monthly, the given cohort is not infectious until the month after it has been infected. Most fish farms raised several fish cohorts during the study period, and are therefore in periods susceptible, infectious or empty (i.e. with no susceptible population at the fish farm).

Let $\lambda_i(t)$ denote the infection rate for a fish farm i at time t. We decompose this infection rate into the contribution from four possible transmission pathways. We assume that conditioned on the history up to time t, disease transmission through each pathway may occur independently of the other pathways. Since the infection rates or intensities are small probabilities, the contributions from the four pathways may then be added to a total infection rate. See Rothman (2002) for a discussion of the importance of additive models when evaluating independent risk factors. In addition, the infection rate for a fish farm i depends on factors describing the susceptibility of the fish farm, and these factors are included as multiplicative terms in the infection rate. The total infection rate for fish farm i at time t has then the following additive-multiplicative structure

$$\lambda_i(t) = S_i(t) \cdot \lambda_b(t) \cdot \lambda_{ix}(t) \cdot [\lambda_i^d(t) + \lambda_i^c(t) + \lambda_i^p(t) + \lambda_i^o(t)]. \tag{1}$$

The three multiplicative terms in Equation (1) are:

1. $S_i(t)$ is an at-risk indicator which is 1 when fish farm i susceptible and 0 else.

2. $\lambda_b(t)$ is a time-varying risk of infection, but constant in space, i.e. common for all fish farms, called the baseline hazard. This term is left unspecified here, and cancels out in the partial likelihood used for estimation (see below).

3. $\lambda_{ix}(t)$ is a factor proportional to the susceptibility of fish farm i, and functionally related to an explanatory variable x that characterises the fish cohort at fish farm i at time t. This factor is present in all the four transmission pathways. The actual formulation of this factor is presented below in Section 4.1.5

The four transmission pathways are:

1. $\lambda_i^d(t)$ - Transmission from other infected fish farms, where the infection rate decreases by increasing seaway *distance* to an infected fish farm.

2. $\lambda_i^c(t)$ - Transmission from infected fish farms in the same local *contact network*.

3. $\lambda_i^p(t)$ - Transmission from *previous* infected fish cohorts at the same fish farm i.

4. $\lambda_i^o(t)$ - Transmission via *other* pathways.

The transmission pathways and expressions for susceptibility and infectiousness are presented in more details in the following sections.

4.1.1 Distance

Transmission from other infected fish farms related to the seaway distance to an infected fish farm includes spread via water, but is not exclusively this route: any other infection mechanism whose risk decreases with distance can be captured with this component. This component can be decomposed further into the sum of contributions from each fish farm j that may infect fish farm i, denoted by $\lambda_{ij}^d(t)$, such that the total relative infection rate $\lambda_i^d(t)$ for fish farm i related to distance is given as $\lambda_i^d(t) = \sum_{j \neq i} \lambda_{ij}^d(t)$, collecting the contribution of every other fish farm.

The relative rate of infection from fish farm j to fish farm i, which is attributed to their seaway distance, is modelled as

$$\lambda_{ij}^d(t) = \exp(-\phi \cdot d_{ij}) \cdot \lambda_{jz}(t) \cdot I_j(t), \tag{2}$$

where

- d_{ij} is the seaway distance between fish farms i and j.
- ϕ is a parameter that expresses the effect of the seaway distance on the risk of infection. The parameter ϕ is restricted to be non-negative, since the risk of infection cannot decrease with decreasing distance between an infectious farm j and a susceptible farm i.
- $\lambda_{jz}(t)$ is a factor proportional to the infectiousness of fish farm j, and is also included in the infection rate related to the contact network, see Section 4.1.2. Its actual formulation in the present application is presented in Section 4.1.5
- $I_j(t)$ is an indicator variable which is 1 if fish farm j is infectious at time t, and 0 otherwise. This variable depends on the time delay, via the definition of events.

4.1.2 Contact network

Transmission from infected fish farms in the same local contact network is possible since such farms are likely to share personnel or equipment. Also this component

can be decomposed into the sum of contributions from each fish farm j, denoted by $\lambda^c_{ij}(t)$, such that $\lambda^c_i(t) = \sum_{j \neq i} \lambda^c_{ij}(t)$.

The relative rate of infection from fish farm j to fish farm i which may be attributed to a shared contact network is modelled similar to Equation (2), but the term $\exp(-\phi \cdot d_{ij})$ in Equation (2) is replaced by a term $\gamma \cdot C_{ij}$ expressing the effect of the contact network as

$$\lambda^c_{ij}(t) = \gamma \cdot C_{ij} \cdot \lambda_{jz}(t) \cdot I_j(t), \tag{3}$$

where, C_{ij} is 1 if the fish farms i and j are in the same contact network, and 0 otherwise. The parameter γ expresses the effect of being in the same contact network. This parameter is restricted to be non-negative, since it is unlikely that the risk of infection decreases when farms within the network are infectious.

4.1.3 Previous infected cohorts

Transmission from a previous infected fish cohort at the same fish farm i may happen if the disease agent remains infective at the farm after the infected cohort has been removed. This transmission pathway is modelled as

$$\lambda^c_{ij}(t) = \kappa \cdot P_i(t), \tag{4}$$

where $P_i(t)$ is an indicator variable which is 1 if there has been a previous infected fish cohort at the same farm i at most six months prior to stocking of the current fish cohort and 0 else. The parameter κ expresses the effect of this rule. This term is analogous to an autoregressive term in time series models. The autoregressive parameter κ is restricted to be non-negative, since we assume that a previous infection at the same farm cannot be protective.

4.1.4 Other transmission pathways

Finally, transmission via other possible pathways accounts for other sources of infection, such as well boats or infected smolts. It can also include infection from other infectious fish farms, but where the infection remained undetected until slaughtering of the cohort. This term accounts for unexplained transmission and plays the same role as the error term in ordinary linear regression. In the present application it is assumed to be constant in time and space, i.e.

$$\lambda^o_i(t) = \theta, \tag{5}$$

where the parameter θ expresses the effect of other transmission pathways. Also, this parameter is restricted to be non-negative, as it represents the positive risk through other transmission pathways.

4.1.5 Susceptibility and infectiousness

In our application, the susceptibility factor $\lambda_{ix}(t)$ is constant over a fish cohort, depending on the category and the size of the cohort. To be specific, it is modelled as

$$\lambda_{ix}(t) = (\beta^a)^{x_i^a(t)} \cdot (\beta^m)^{x_i^m(t)} \cdot (\beta^r)^{x_i^r(t)} \cdot (x_i^n(t))^{\beta^n}. \tag{6}$$

Here the binary variables $x^a(t)$, $x^m(t)$ $x^r(t)$ are 1 if the cohort is an autumn, a mixed or a relocated cohort, respectively. If it is a spring-cohort, all these three variables are 0. The three first β-parameters measure the susceptibility of each type of cohort relative to a spring-cohort, i.e. the relative risk. For instance, for a spring-cohort the relative risk is 1, whereas for an autumn-cohort it is equal to β^a. Furthermore, $x_i^n(t)$ is the maximum number of fish in cohort i, measured in millions, during the production period, usually the number of fish at stocking. Biomass could be an alternative measure of cohort size. In contrast to Scheel et al. (2007), we use a time-constant measure of cohort size, since time-varying measures would be confounded with alternative explanatory variables such as time since stocking. The coefficient β^n measures the effect of the number of fish on the cohort susceptibility. Note that by re-parameterising the three relative risk parameters, $\lambda_{ix}(t)$ can equivalently be written in exponential form as

$$\lambda_{ix}(t) = \exp\left[\beta^{*a} x_i^a(t) + \beta^{*m} x_i^m(t) + \beta^{*r} x_i^r(t) + \beta^n \log\left(x_i^n(t)\right)\right], \tag{7}$$

It is in fact this expression that is used in the estimation procedure described below, and the relative risk coefficients are found as the exponential of the β^* parameters as $\beta^a = \exp(\beta^{*a})$, $\beta^m = \exp(\beta^{*m})$ and $\beta^r = \exp(\beta^{*r})$, which ensures that the three relative risk coefficients are positive.

The infectiousness factor $\lambda_{jz}(t)$ is simpler, and depends only on the size of the fish cohort at fish farm j at time t as

$$\lambda_{jz}(t) = (z_i^n(t))^{\alpha^n}, \tag{8}$$

where $z_j^n(t) = x_j^n(t)$ is the maximum number of fish in cohort j during the production period, and the coefficient α^n expresses the effect of the number of fish on the infectiousness.

4.1.6 Full model

The specific version of the generic model 1 that is used in this paper can now be written in detail as

$$\lambda_i(t) = S_i(t) \cdot \lambda_b(t) \cdot (\beta^a)^{x_i^a(t)} \cdot (\beta^m)^{x_i^m(t)} \cdot (\beta^r)^{x_i^r(t)} \cdot (x_i^n(t))^{\beta^n} \cdot \tag{9}$$
$$\left[\sum_{j \neq i} \{\exp(-\phi \cdot d_{ij}) \cdot (z_j^n(t))^{\alpha^n(t)} \cdot I_j(t)\} + \sum_{j \neq i} \{\gamma \cdot C_{ij} \cdot (z_j^n(t))^{\alpha^n(t)} \cdot I_j(t)\} + \kappa \cdot P_i(t) + \theta\right].$$

4.2 Parameter estimation

We estimate the unknown parameters ϕ, γ, κ, θ, the four β's and α^n by maximum partial likelihood (Cox 1975, Diggle 2006). Let T denote the list of distinct event times. Further, let All denote the list of all fish farms and $Inf(t)$ the list of fish farms that become infected at time t, which is at least 1 for each event time. The ordinary partial likelihood is then

$$\prod_{t\in T}\prod_{i\in Inf(t)}\frac{\lambda_i(t)}{\sum_{k\in All}\lambda_k(t)}. \tag{10}$$

Each term in the partial likelihood can be interpreted as the conditional probability that fish farm i becomes infected at time t, given that one farm gets infected at time t.

Since the data has a monthly resolution there are months with more than one event, also denoted as ties. To correct for ties in the partial likelihood we use Efron's (1977) method, and estimate the parameters by maximising the following partial likelihood corrected for ties

$$\prod_{t\in T}\prod_{i\in Inf(t)}\frac{\lambda_i(t)}{\sum_{k\in All}\lambda_k(t)-f(t,i)\sum_{k\in Inf(t)}\lambda_k(t)}. \tag{11}$$

Here, $f(t,i)$ is the correction factor for ties given by

$$f(t,i) =(m(i)-1)/n(t), \tag{12}$$

where $n(t)$ is the number of events (number of fish farms infected) at time t, and $m(i)$ is the index number of fish farms i in the list $Inf(t)$, i.e. $m(t)$ is 1 for the first fish farm in the list, and then consecutive numbers for each fish farm in the list until $n(t)$ for the last fish farm. If, for instance, there are three fish farms that become infected at time t, $f(t,i)$ take the values 0, 1/3 and 2/3 for this event time. The order of the fish farms is arbitrary.

The partial likelihood is maximised using the method of Byrd et al. (1995) for constrained optimisation implemented in the function *optim* in the statistical software *R*, with the parameters ϕ, γ, κ and θ constrained to be non-negative. Parameter uncertainties are based on the observed Fisher information matrix (see for example Pawitan 2001). This is not reliable when the constrained parameters are at or close to the range boundaries. Therefore, when this happens, the constrained parameters are fixed at the boundary, and the Fisher information matrix is recalculated. The measured relative importance of the various transmission pathways, defined in Section 4.3, are functions of the basic model parameters. To estimate their uncertainties we perform Monte Carlo simulations by sampling the basic model parameters from their asymptotic multivariate normal distribution.

The parameter uncertainties are reported as 95 % confidence intervals. In addition, hypothesis test for the parameters being different from 0 are performed. Hypothesis tests for the four parameters restricted to be non-negative (ϕ, γ, κ and θ) are one-sided, the others tests are two-sided, all with 5 % significance level. Recall the equivalence between confidence intervals and p values: If 0 (the null hypothesis) lies outside the interval, the corresponding two-sided p value is less than 0.05 and the one-sided p value is less than 0.025.

4.3 Parameter interpretation and relative importance of transmission pathways

The parameters ϕ, γ, κ and θ must be interpreted relative to each other for each disease, and together with α^n and the cohort size $z_j^n(t)$ at an infectious cohort. When the distance between two fish farms is 0, the expression $\exp(\phi \cdot d_{ij})$ is 1. Thus, when γ is larger than 1, being in the same contact network with *one* infectious fish farm gives a higher contribution to the total infection rate than having *one* infectious fish farm infinitesimally close. Furthermore, having an infectious fish farm at a seaway distance of $d_{ij} = -\log(\gamma)/\phi$ has the same effect as sharing the contact network with an infectious fish farm. Having an infectious fish farm with cohort size z_j^n at a seaway distance of $d_{ij} = (\alpha^n \log(z_j^n) - \log(\kappa))/\phi$ has the same effect as having a previous infectious fish cohort at the same fish farm and a distance $d_{ij} = (\alpha^n \log(z_j^n) - \log(\theta))/\phi$ has the same effect as other transmission pathways.

These interpretations of the parameters, though interesting per se, do not take into account the number of infectious fish farms in the neighbourhood or within a contact network of a susceptible fish farm, which certainly affects the infection rate. To also account for this, we calculated the relative importance of each of the transmission pathways. This was done by calculating the proportion of the infection rate for each event associated with each transmission pathway, and then averaging over all events. For instance, we calculate the relative importance of the transmission related to distance by

$$\frac{1}{\text{total number of events}} \sum_{t \in T} \sum_{i \in Inf(t)} \frac{\lambda_i^d(t)}{\lambda_i^d(t) + \lambda_i^c(t) + \lambda_i^p(t) + \lambda_i^o(t)}. \tag{13}$$

5 Results

We estimated the transmission model for each of the three diseases separately, using all outbreaks recorded in the period 2004-2007 as events in the partial likelihood given by Equation (11). There were 326, 209 and 38 events for the diseases HSMI, PD and ISA, respectively. The outbreaks in 2003 were used to initialize the statistical model for outbreaks recorded from 2004 onwards. For PD, which is a disease of both Atlantic salmon and rainbow trout, the model was fitted to data from all 1082 fish farms, and the number of fish in each fish cohort was the sum of salmon and rainbow trout. Salmon and rainbow trout were treated equally in the model, in accordance to Kristofferson et al. (2009) who found no significant difference in susceptibility among the two species. For HSMI and ISA, which only infect salmon, rainbow trout data were ignored, reducing the number of fish farms to 1035, and reducing the number of fish for those farms that produced both species.

Table 1 shows the estimated parameter values with 95 % confidence intervals, when the time delay was assumed to be 6 months. The results for time delays equal to 3, 9 or uniform between 3 and 9 months were similar (not reported, but available from the authors). The ϕ parameter, measuring the effect of the distance to an infectious fish farm, was positive and significant for all three diseases (all p values less than 0.002). For a better understanding of the estimates of ϕ, as well as γ, κ and θ, see Figure 2. For HSMI, the estimated ϕ parameter seems small, but corresponds in the first panel of Figure 2 to a relative infection rate curve of distance which decays slowly. This indicates a longer transmission range of the disease. For ISA, this range was much shorter. The contact network parameter (γ) was positive and significant for HSMI (p value 0.03) and PD (p value 0.01) and exactly 0 for ISA. The autoregressive parameter (κ) was positive and significant for HSMI (p value 0.02) , but 0 for the two other diseases. The θ parameter, describing other non-specified transmission pathways, was positive and significant for all three diseases (p values 0.01 for HSMI, 0.03 for PD and 0.02 for ISA).

The effect of the time of stocking was measured by the three relative risk parameters β^a, β^m and β^r. For HSMI, autumn cohorts had significantly higher infection rates than spring cohorts (the reference), whereas relocated cohorts had significantly lower infection rates. For PD, the difference between autumn and spring cohorts was non-significant, but both relocated and mixed cohorts had significantly lower infection rates than autumn as well as spring cohorts. For ISA there was no significant differences between the four types of cohorts.

The β^n parameter was positive and significant for all three diseases, which means that the susceptibility increased by increasing cohort size at the susceptible farms. Correspondingly, infectiousness tended to increase by increasing cohort size at the

infectious farms, but this effect (α^n) was only significant for PD and ISA.

The estimated relative infection rates of the four different transmission pathways are given in in Figure 2. For seaway distance and contact network comparisons are for the risk related to *one* infectious fish farm with a typical size of infectious cohorts of 0.88 million fish. Considering HSMI first, having a previous infectious cohort at the same fish farm was the most important single risk factor. Furthermore, having one infectious fish farm in the same contact network contributed more to the infection rate than having one infectious fish farm at any distance, also very close. Also, being in the same contact network as one infectious fish farm was more risky than any other non-specified transmission pathway. Furthermore, having an infectious fish farm closer than about 18 km (in dashed blue) represented a higher risk than other non-specified transmission pathways.

The panels for the other diseases in Figure 2 are interpreted similarly. For PD, having one infectious fish farm in the same contact network corresponded to having one infectious fish farm at a distance 8 km (in dashed red). A distance of 49 km (blue) represented the same risk as other non-specified transmission pathways. For ISA, having an infectious fish farm at a distance of 11 km (blue) represented the same risk as other non-specified transmission pathways. This means that an infected fish farm was highly infectious in a small range, as seen by the distance curve being much higher than for the other effects. But the curve decays very rapidly, showing that the other non-specified transmission pathways dominated after 11 km.

To illustrate the relative importance of the various transmission pathways we computed the relative imortance (see Equation (13)) of each transmission pathway averaged over all outbreaks during 2004-2007 (Table 2). This was calculated for fixed time delays of 3, 6 and 9 months, and for random time delays uniformly distributed between 3 and 9 months. Conclusions were rather insensitive to the different time delay values within the given range. For HSMI, and especially PD, transmission related to the distance from an infectious fish farm dominated, but transmission related to the contact network was also of some importance. For HSMI, transmission from previous infected cohorts at the same fish farm also had some effect. For ISA, about 80 % of the outbreaks were attributed to other non-specied transmission pathways, whereas about 20 % were attributed to distance.

Results in Table 2 are not contradictory to Figure 2. For HSMI, having a previous infectious cohort at the same fish farm represented the highest single risk. However, only 16 % of cohorts with outbreaks of HSMI were exposed to that risk in the actual data. Furthermore, sharing contact network with one infectious fish farm represented a higher risk than being close to an infectious farm. However, in the actual data, an infected fish farm was frequently located in proximity, but less frequent in a shared contact network. Contact networks were relatively small and

not connected. Hence, spread of a disease within networks was limited. Therefore, in the historical data seaway distance represented 54 % of the total risk, although having a previous infectious cohort at the same fish farm and sharing contact network with an infectious fish farm represented higher single risks.

The determination of true infection times, although the relevant biological event, is often difficult in epidemiological studies based on surveillance data. When the model analysis was repeated based on notification time instead of infection times, the results were found qualitatively similar (data not shown).

6 Discussion

In this paper we applied a statistical spatio-temporal model for the transmission of infectious diseases among fish farms. The infection rate for a farm is decomposed into contributions related to distance to adjacent infectious farms, infectious farms in the same local contact network, previous infectious fish cohorts at the same farm and other transmission routes. In addition, the statistical model contains a time-varying term common for all farms, one term that characterises the susceptible farm and finally one term that characterises an infectious farm. The statistical model was applied to three different diseases (HSMI, PD and ISA) in Norwegian fish farms.

The comparison of the space-time dynamics of disease outbreaks of the three diseases revealed specific differences that have important implications for management practices. For PD, transmission was well explained by seaway distance ($\sim$80%), whereas the contribution from the non-specified other pathways was low ($\sim$5%). This, we believe, reflects extensive local transmission of the causative agent SAV between neighbouring farms, which is also in agreement with earlier studies (Fringuelli et al., 2008; Kristoffersen et al. 2009). Hence, control should focus on bio-security measures aimed at reducing the probability of farm to farm transmission of SAV. Compared to ISA, the relative effect of seaway distance to infectious farms for PD seems to have a longer range. We do not know the actual transmission pathway, or pathways, that are captured by the effect of seaway distance. One possibility is simply by passive drift of SAV in the water current from infectious farms. Laboratory studies on the biophysical properties of SAV suggests that the virus is capable of surviving for extended periods of time in the aquatic environment, and supports the hypotheses that SAV may transmit by passive drift between farms (Graham et al. 2007). There are, however, other possible pathways of transmission between farms for which the risk may be expected to increase with proximity between infectious and susceptible farms, e.g. transmission through wild fish or escaped farmed fish.

For ISA the relative contribution from the non-specified other pathways was especially high (70-80%). This reflects a dynamic pattern where most outbreaks occur isolated in space and time, but where occasionally also small space-time clusters of outbreaks occur (Scheel et al. 2007; Lyngstad et al. 2008). The failure of the present statistical model in assigning specified transmission pathways for ISA emphasises that there is some fundamental mechanisms of transmission and properties of the ISA-virus that are not understood. Evidence now points to the existence of non-virulent strains of ISAV together with virulent strains of the virus, and where specific mutations distinguishing between non-virulent and virulent strains have been suggested (Markussen et al., 2008). Such non-virulent ISAV have been suggested to transmit vertically from parent fish to offspring (Nylund et al. 2007, Vike et al. 2009). This indicates that isolated ISA out-

breaks may arise from mutations of non-virulent ISAV, and that ISAV infection may be hidden while it does not manifest in recorded disease. Nevertheless, the tendency for ISA outbreaks to partly occur in small clusters, which is captured by the significant effect of the seaway distance pathway in the present statistical model, suggest that farms that acquire ISA represents a risk of transmission to susceptible adjacent farms. The distances over which such transmission may occur are, however, indicated to be over shorter ranges for ISA compared to the other diseases in the present statistical model.

Characteristic for HSMI was an effect of previous infected cohorts on given farms and indications of a comparably long range of seaway transmission. The estimated contribution of the contact network transmission pathway was relatively high. Since the infectious agent causing HSMI is unknown, it is tempting to speculate on what characteristics of the disease agent would give rise to the observed pattern of disease outbreaks. Compared to the local farm to farm transmission dynamics which apparently dominates for PD, the transmission pathways for HSMI tend to suggest that there is some external source of infection involved. Such an external source could for instance be that smolts are infected in freshwater prior to movement to sea cages. This would hypothetically give the same effect of contact network and previous infected cohorts in the present statistical model, provided that farms within networks tend to purchase smolts from the same sources. Transmission in freshwater is a key pathway for transference of infectious pancreas necrosis (IPN) to marine salmon farms (Murray 2006, Ruane et al. 2009). Even though the proposal of an external source of infection is speculative, we argue that the present analysis does provide insight into the spread of HSMI and that a contagious nature of the disease is supported (Kongtorp et al. 2004a). Given the high abundance of HSMI outbreaks, and the lack of knowledge regarding the infectious agent of the disease, the present prospects of controlling HSMI seem difficult. One specific tendency in the present data which is worth considering is that the risk of contracting HSMI doubles in autumn cohorts of smolts compared to spring cohorts.

The present statistical model has potentially several areas of utilisation. It may be used to substantiate transmission pathways and risk factors for disease, as in the present application. It may also be used as a simulation tool to test effects of various control strategy scenarios. Of the present diseases, PD would be most suitable for such an approach since a comparably large part of the outbreaks are assigned to specified transmission pathways in the statistical model. Also, due to the large numbers of outbreaks the statistical model can be estimated precisely. Of special interest would be simulations of various scenarios with regard to geographic location of fish farms, as well as effects of vaccination. However, for this particular use also the baseline hazard ($\lambda_b(t)$) has to be modelled and estimated. More specifically, in order to study new scenarios, it would be necessary to sample from the estimated full likelihood. The partial likelihood is not a full

probabilistic model, and hence cannot be used for simulation directly.

The statistical model, extending the previous approach of Scheel et al. (2007), is supported by biological and fishery-organisational plausibility, but remains otherwise externally unvalidated.

The statistical model may also be extended in several ways. Perhaps the most important improvement would be to take into account that a farm may be infectious, but the infection was never detected because the cohort was terminated soon after the infection event. The statistical model can also be extended to allow for recovery from disease before the cohort is slaughtered. Another useful extension would be to take into account the genotype of the virus, which is possible for the ISA virus (see for instance Lyngstad et al. 2008). Moreover, from 2007 an increasing proportion of cohorts has been vaccinated against PD (http://www.kyst.no/index.php?page_id=95&article_id=82323). By collecting disease history and the vaccine information for each cohort, the present statistical model approach may be applied to study the potential effect of the PD vaccine on the infection rate.

7 Conclusion

Stochastic models, like in Scheel et al. (2007) can be used to study different transmission patterns of infectious diseases between fish farms. In particular they can be used to compare transmission pathways of different diseases, by quantifying the risk for a susceptible unit, produced by an infectious unit (here fish farm) within one out of many possible pathways.

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Table 1: Estimated parameters with 95 % confidence intervals for the model of eqation (9), assuming the time delay to be 6 months, for outbreaks of HSMI, PD and ISA at Norwegian fish farms between 2003 and 2007.

Parameters		HSMI			PD			ISA		
			95 % conf.int.			95 % conf.int.			95 % conf.int.	
Effect of	Symbol	Est.	Lower	Upper	Est.	Lower	Upper	Est.	Lower	Upper
Seaway distance	ϕ	0.039	0.014	0.064	0.082	0.057	0.108	0.42	0.22	0.62
Contact network	γ	1.45	-0.02	2.91	0.52	0.08	0.96	0	-	-
Previous inf.	κ	6.30	0.26	12.35	0	-	-	0	-	-
Other	θ	0.41	0.08	0.73	0.012	0.000	0.023	0.003	0.001	0.006
Autumn cohort	β^a	1.89	1.44	2.48	1.16	0.84	1.61	0.24	0.05	1.14
Mixed cohort	β^m	0.74	0.52	1.05	0.53	0.34	0.82	0.80	0.35	1.85
Relocated cohort	β^r	0.46	0.32	0.67	0.45	0.29	0.70	0.64	0.27	1.53
Susc. cohort size	β^n	0.54	0.33	0.76	0.44	0.19	0.69	0.62	0.08	1.15
Inf. cohort size	α^n	0.34	-0.34	1.03	0.77	0.23	1.31	2.00	0.52	3.47

conf.int.: confidence interval
Est.: Estimate
Susc.: Susceptible
Inf.: Infectious

Table 2: The relative importance (in %) of each transmission pathway, for time delays assumed to be fixed 3, 6 or 9 months or random and uniform between 3 and 9 months, for outbreaks of HSMI, PD and ISA at Norwegian fish farms between 2003 and 2007, relative to the estimated model in equation (9).

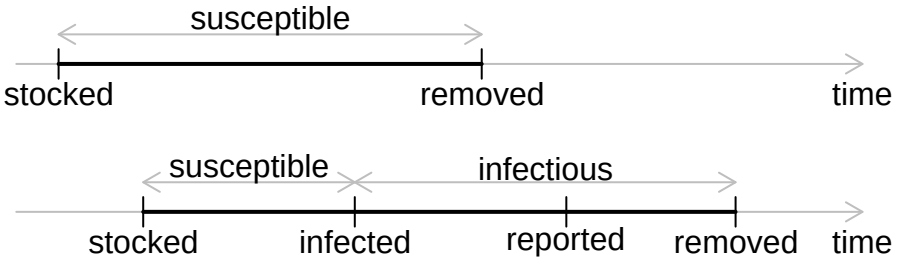
		HSMI			PD			ISA		
	Time		95 % conf.int.			95 % conf.int.			95 % conf.int.	
Pathway	delay	Est.	Lower	Upper	Est.	Lower	Upper	Est.	Lower	Upper
Seaway distance	3	62	54	76	80	75	92	21	15	50
Contact network	3	16	2	22	16	4	21	12	0	14
Previous inf.	3	4	0	5	0	-	-	0	-	-
Other	3	18	10	25	4	1	7	67	50	73
Seaway distance	6	54	47	79	80	74	91	22	21	37
Contact network	6	18	0	24	16	4	22	0	-	-
Previous inf.	6	9	0	10	0	-	-	0	-	-
Other	6	19	9	24	4	0	6	78	63	79
Seaway distance	9	50	43	73	76	69	88	22	20	37
Contact network	9	20	2	26	20	6	25	0	-	-
Previous inf.	9	11	2	12	0.3	0	2	0	-	-
Other	9	19	10	25	4	1	7	78	63	80
Seaway distance	Uni(3,9)	56	48	78	80	74	90	22	20	40
Contact network	Uni(3,9)	18	0	24	16	6	21	0	-	-
Previous inf.	Uni(3,9)	8	1	10	0	-	-	0	-	-
Other	Uni(3,9)	18	8	24	4	1	7	78	60	80

conf.int.: confidence interval
Est.: Estimate
Previous inf.: Previous infected cohort at the same farm
Uni(3,9): Uniform between 3 and 9

FIGURES

Figure 1: Illustration of susceptible and infectious fish cohorts, infection time, outbreak time and time delay.

Figure 2: Estimated relative infection rates for i) *one* infected neighbouring fish farm with a typical cohort size (solid black), ii) *one* fish farm in the same contact network, with a typical cohort size (solid red), iii) a previous infected cohort at the same farm (solid green) and iv) other transmission pathways (solid blue). The red dashed vertical line is the distance where an infected fish farm with a typical cohort size has the same effect as being in the same contact network as one infected fish farm. The blue dashed vertical line is the distance where an infected fish farm with a typical cohort size has the same effect as the transmission from other transmission pathways.


susceptible
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infected
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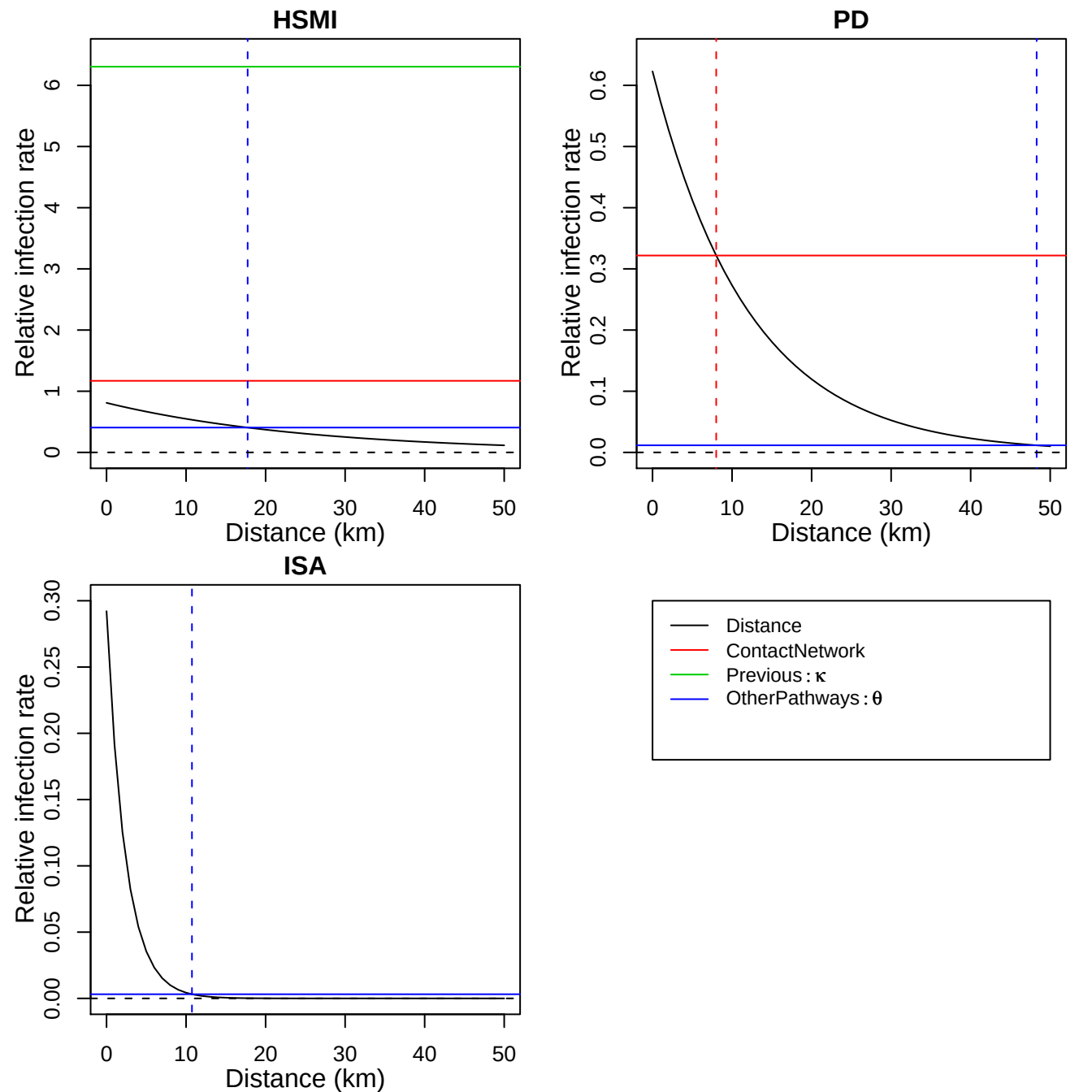
time


HSMI
PD
ISA
Relative infection rate
Distance (km)
0
10
20
30
40
50
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.00
0.05
0.10
0.15
0.20
0.25
0.30
1
2
3
4
5
6
Distance
ContactNetwork
Previous : κ
OtherPathways : θ