JOURNAL OF THE ROYAL SOCIETY Interface

A stochastic model for infectious salmon anemia (ISA) in Atlantic salmon farming

Ida Scheel, Magne Aldrin, Arnoldo Frigessi and Peder A Jansen

J. R. Soc. Interface 2007 **4**, 699-706
doi: 10.1098/rsif.2007.0217

JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2007) **4**, 699–706
doi:10.1098/rsif.2007.0217
Published online 13 February 2007

A stochastic model for infectious salmon anemia (ISA) in Atlantic salmon farming

Ida Scheel[1,*], Magne Aldrin[2], Arnoldo Frigessi[3] and Peder A. Jansen[4]

[1]*Department of Mathematics and (sfi)²- Statistics for Innovation, University of Oslo, PO Box 1053 Blindern, 0316 Oslo, Norway*
[2]*Norwegian Computing Center and (sfi)²- Statistics for Innovation, 0314 Oslo, Norway*
[3]*(sfi)²- Statistics for Innovation and Department of Biostatistics, University of Oslo, PO Box 1122 Blindern, 0317 Oslo, Norway*
[4]*Section of Epidemiology, National Veterinary Institute, PO Box 8156 Departmental Division, 0033 Oslo, Norway*

Infectious salmon anemia (ISA) is one of the main infectious diseases in Atlantic salmon farming with major economical implications. Despite the strong regulatory interventions, the ISA epidemic is not under control, worldwide. We study the data covering salmon farming in Norway from 2002 to 2005 and propose a stochastic space-time model for the transmission of the virus. We model seaway transmission between farm sites, transmission through shared management and infrastructure, biomass effects and other potential pathways within the farming industry. We find that biomass has an effect on infectiousness, the local contact network and seaway distance of 5 km represent similar risks, but a large component of risk originates from other sources, among which are possibly infected salmon smolt and boat traffic.

Keywords: biomathematics; infectious disease dynamics; spatio-temporal point processes; partial likelihood; infectious salmon anemia virus; Atlantic salmon farming

1. INTRODUCTION

World aquaculture has grown tremendously in recent decades and, along with this, a number of new diseases caused by pathogens of a wide taxonomical diversity have emerged (Murray & Peeler 2005). Infectious salmon anemia (ISA) is an infectious disease of farmed Atlantic salmon (*Salmo salar*). Atlantic salmon farming has been a rapidly growing industry in Norway since the beginning of the 1970s, producing 582 000 tonnes of fish with a first hand value of $1.8 billion in 2005 (Statistics-Norway 2006), making Norway a leading producer. Since the first outbreak of ISA in 1984, in Norway, the virus has caused large economic damage in the salmon farming industry in Europe and North America. Control strategies have not yet succeeded in eradicating ISA, except in Scotland (Stagg *et al.* 2001), therefore, it is important to identify the factors affecting the transmission of the ISA virus (ISAV). In this paper, we present a stochastic space-time model for the spread of ISA in Norway during 2002–2005.

Stochastic modelling of human and veterinary infectious diseases is a field of increasing importance. Keeling *et al.* (2001) modelled the foot-and-mouth epidemic in UK livestock suggesting that the most important factor in the dispersal was the distance between farms. The spread of disease in aquaculture systems is a developing field of research as witnessed by recent papers (Murray 2006; Sharkey *et al.* 2006; Thrush & Peeler 2006). Transmission pathways for ISAV and risk factors for ISA outbreaks are still unclear. We propose a stochastic model inspired by Keeling *et al.* (2001) and Diggle (2006), which captures the relative importance of the main risk factors associated with different pathways of transmission. The model investigates the relative importance of proximity to an infectious farm site by seaway distance and local contact network on the rate of transmission, as well as the importance of farm site biomass on infectiousness and susceptibility. The model also compares the rate of transmission from infectious farm sites to the rate of transmission through other potential pathways within the Norwegian salmon farming industry. The model allows precise interpretations of the parameters. We have applied the model to a unique dataset, covering the whole ISA history in Norway over the years 2002–2005 and all farm sites with a recorded biomass at any time point during this period. The dataset contains location and biomass reports from 1035 farm sites and 41 ISA infection reports. The results reveal that the majority of the total risk is likely to originate from sources other than infectious farm sites. Furthermore, seaway distance and local contact networks explain the same amount of the total risk, although having an infectious farm site at a distance from 0 to 5 km implies more risk of being infected than being in the same local contact network with an infectious farm site. The results also show

*Author for correspondence (idasch@math.uio.no).

Received 13 December 2006
Accepted 12 January 2007

that the biomass seem to have an effect on infectiousness. Our findings challenge the efficiency of currently implemented monitoring and regulation strategies.

2. HISTORY AND EPIDEMIOLOGY OF ISA

The first recorded outbreak of ISA occurred in 1984 in Atlantic salmon parr in a hatchery on the southwest coast of Norway (Thorud & Djupvik 1988). The disease has since been reported in Atlantic Canada (1996; Mullins *et al.* 1998); Scotland (1998; Rodger *et al.* 1998); the Faroe Islands (1999; Lyngøy 2003); Chile (1999; Kibenge *et al.* 2001) and Maine, USA (2000; Bouchard *et al.* 2001). Except Chile, all these areas have experienced ISA epidemics of varying scales.

ISA is caused by a viral pathogen (ISAV) of the Orthomyxoviridae family (Krossøy *et al.* 1999). The disease is characterized by lethargy, anorexia, anemia and varying degrees of mortality (Thorud 1991). In general, clinical ISA has been associated with seawater farmed Atlantic salmon. However, Kibenge *et al.* (2001) isolated ISAV from clinically sick farmed Coho salmon (*Oncorhynchus kisutch*) from Chile. The virus has also been shown to be capable of replication in brown trout (*Salmo trutta*) (Nylund *et al.* 1995) and rainbow trout (*Oncorhynchus mykiss*) (Snow *et al.* 2001). Wild Atlantic salmon and wild brown trout have been found to be infected with ISAV (Plarre *et al.* 2005).

In Norway, the number of seawater Atlantic salmon farm sites with verified ISA outbreaks increased steadily from the first occurrence in 1984 to a peak in 1990, when 80 ISA cases were verified. By 1992, ISA outbreaks occurred along most of the Norwegian coast (Jarp & Karlsen 1997). The number of ISA outbreaks reduced to only one in 1992 and two in 1993. This pronounced reduction has been attributed to the implementation of various preventive measures (Thorud & Håstein 2003). Later, the number of ISA outbreaks has increased moderately; between 6 and 23 cases annually from 1997 to 2004, widespread over the coast (Kvellestad *et al.* 2005). The current policy regarding minimum distance between seawater salmon farming sites is 2.5 km. Historically this has not always been followed, implying that sites may have been located closer to each other.

Thorud & Håstein (2003) describe the regulatory responses to ISA in Norway. In 1991, regulations on disinfection of effluents and secure treatment of offal from slaughtering houses and processing plants were implemented. In 1996, the authorities introduced official guidelines to deal with the outbreaks of ISA. Among others, the guidelines directed prompt destruction of fish in cages with confirmed ISA diagnosis and in other cages with clinically diseased fish, and then a full eradication out of the fish population within 80 working days followed by a fallowing period on the site. These practices have been the regulation throughout the study period 2002–2005.

Epidemiological studies conducted in Norway identified proximity to other farm sites with ISA outbreaks as a significant risk factor. These studies indicated that seawater constituted a major pathway for the transmission of ISAV and that the virus may disperse passively with the water current through normal discharge from ISAV-infected farm sites (Vågsholm *et al.* 1994; Jarp & Karlsen 1997). Proximity to infected farm sites has later been confirmed as a risk factor by epidemiological studies in Canada (Gustafson *et al.* 2005; McClure *et al.* 2005). Laboratory studies have also shown that the virus can disperse through seawater (Løvdal & Enger 2002). In Norway, different farm sites with common ownership may be operated by shared staff and boats, and often from a shared wharf. Hence, there is a local contact network between farm sites described by ownership. Epidemiological studies have identified a number of farm site management and husbandry-related risk factors for ISA outbreaks, e.g. shared staff between the farm sites, divers visiting the multiple farm sites, low frequency of the removal of dead fish and low rate of treatment against sea lice (Jarp & Karlsen 1997; Hammell & Dohoo 2005; McClure *et al.* 2005). Low density of fish in cages has been shown to reduce the susceptibility (Hammell & Dohoo 2005), but the impact of fish population size on site infectiousness and susceptibility is still unclear. Other pathways than farm-to-farm transmission have been suggested. These involve infected juvenile fish (smolt) (Nylund *et al.* 2007), shipment of live fish (Murray *et al.* 2002) and transmission facilitated by various harvesting methods (Munro *et al.* 2003). The importance of transmission of ISA from infectious farm sites relative to the transmission from other sources such as infected smolt and well boats is not known.

3. DATA

3.1. ISA-infected farm sites

The ISA-infected sites were identified at the National Veterinary Institute (NVI), Norway, which acts as a national and international reference laboratory for ISA diagnostics. ISA is classified as a B-category infectious disease in Norway and a list 1 disease in the EU under the Council Directive 91/67/EEC. Fish samples from all suspected outbreaks are analysed at NVI. Confirmation of a diseased population is based on a combination of clinical signs and diagnostic tests. For case sites in the present study, we used the date that fish samples were received and registered at NVI as the date of detection of ISA on the premises. There is one tie in the data, i.e. on one date there are two reported outbreaks at two different sites. The slaughtering time points were given with an approximation of three months.

3.2. Farm site biomass

The Atlantic salmon farming production cycle comprise a freshwater phase in which the fish are reared from eggs to the smolt stage, followed by a seawater phase in which smolt are moved to seawater farm sites and ongrown until slaughtering. All the outbreaks of clinical ISA have been associated with the seawater phase or the use of part seawater in freshwater hatcheries (Stagg *et al.* 2001). Our data include Norwegian fish farm sites (sites) in seawater with a standing stock of Atlantic salmon recorded at any point in time during the study period.

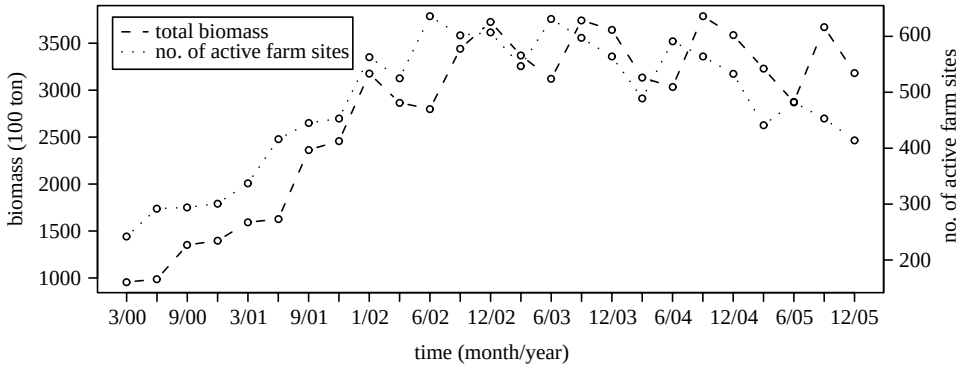


Figure 1. Total biomass (100 ton) of Atlantic salmon (left axis) and the number of active sites along the Norwegian coast (right axis) for the period 2000–2005. On 1 January 2002, there was a change in the license register identification system, making it impossible to use full data for the years 2000 and 2001.

Table 1. Summary of the distributions of quarterly reports on site-specific biomass, seaway distances and the sizes of the local contact networks for the years 2002–2005.

variable	min.	first percentile	fifth percentile	first quartile	mean	median	third quartile	max.
biomass (100 ton)	0.0	0.1	0.3	1.8	6.1	4.4	8.8	43.4
seaway distance (km)	0.2	18.8	61.5	100.0	96.0	100.0	100.0	100.0
size of local contact networks	1	1	1	2	2.8	3	3	11

Every operator of a site holding the salmonids is required to report key production statistics on a monthly basis to the Directorate for Fisheries (DFF). We have reports on biomass on all the active sites along the Norwegian coast on a quarterly basis starting from March 2000 to December 2005, and an additional report from January 2002. Figure 1 shows the number of farms and total biomass for the period. The level change in January 2002 is artificial due to a systematic change in the license register identification system and in the procedures followed for reporting. Before 2002, the operating companies sent joint reports comprising several sites, using a different identification system for each site. When merging the old system with the new one, we could not identify the location number between 13 and 26% of the sites each quarter (overall mean 20%, decreasing in time, which explains the increasing level from March 2000 to December 2001), despite that these had a standing stock of salmon in 2000–2001. In addition, there seems to have been substantial underreporting of biomass in 2000–2001. We therefore discarded the years 2000 and 2001 in our analysis. A summary on the distribution of quarterly reports on site-specific biomass for 2002–2005 can be seen in table 1.

3.3. Seaway distances between sites

The seaway distance (the shortest distance over seawater in kilometres) between farm sites within 100 km of each other was computed using the ArcView extension Spatial Analyst (ESRI, Redlands, CA, USA). The geographical coordinates of the sites were obtained from the aquaculture license register of DFF (www.fiskeridir.no). Distances larger than 100 km are set to infinity. A summary of the distribution of the seaway distances between the sites can be seen in table 1.

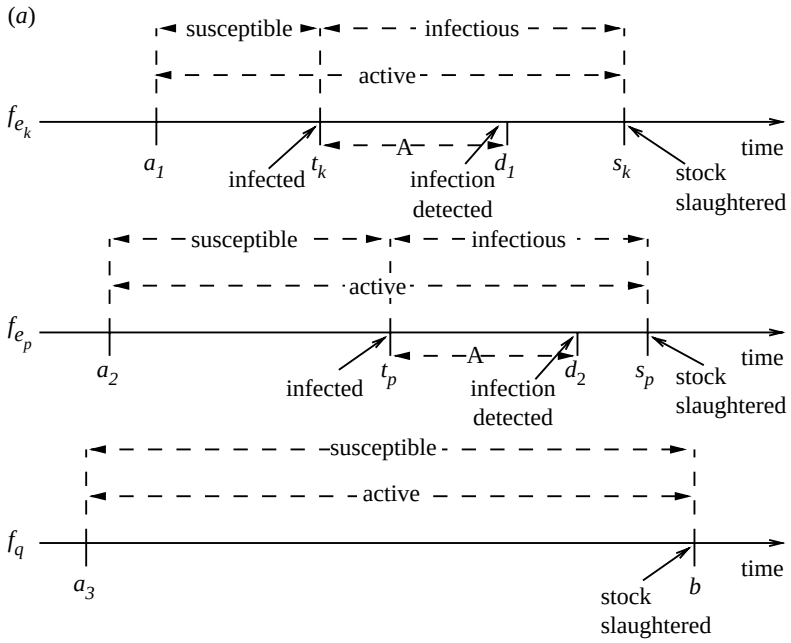
3.4. Local contact networks

Operators of fish farming sites in Norway are predominantly companies that operate many sites. Locally, the same team of workers may operate different sites and often from a shared wharf. In addition, the sites operated by the same company may share equipment, boats, etc. This implies that sites appear in networks of contact locally. To approximate such local contact networks, a variable was compiled from the aquaculture license register identifying sites with shared ownership within municipalities. Out of a total of 431 municipalities in Norway, sites were registered in 173 municipalities. We retrieved ownership from the license register only from one point in time (September 2004) and assumed that this reflects the ownership structure throughout the study period. The variable is an approximation to the effective local contact networks, which may lead to an underestimation of this effect. A summary of the distribution of the sizes of the contact networks can be seen in table 1. Table 2 shows the size of the local contact networks to which the ISA outbreak farms belong to.

4. A STOCHASTIC SPACE-TIME MODEL

4.1. Model specification

In this section, we describe a mathematical model for the probability that a susceptible site is infected at a time point t, as a function of several observable covariates: the biomass standing on the site at time t, the biomass of an infectious site from which the virus might potentially originate at time t, the distance between these two sites and the local networks they belong to. In addition, we allow for a further transmission pathway along routes which are not



(b)

	start of time interval									
	a_3	a_2	a_1	t_k	t_p	d_1	d_2	s_k	s_p	b
$I_{e_k e_p}$	0	0	0	1	0	0	0	0	0	0
$I_{e_p e_k}$	0	0	0	0	0	0	0	0	0	0
$I_{e_k q}$	0	0	0	1	1	1	1	0	0	0
$I_{q e_k}$	0	0	0	0	0	0	0	0	0	0
$I_{e_p q}$	0	0	0	0	1	1	1	1	0	0
$I_{q e_p}$	0	0	0	0	0	0	0	0	0	0

Figure 2. Illustration of definitions 1–5 and of the indicator function $I_{ji}(t)$ in equation (4.1). (*a*) The status is shown for two sites experiencing events (f_{e_k} and f_{e_p}) and one site where there is no event (f_q). Site f_{e_k} is susceptible from time a_1 until it becomes infected at event time t_k. The infection is detected at time d_1. Site f_{e_k} is infectious from time t_k until time s_k when the stock is slaughtered and the site becomes inactive. Site f_{e_p} is susceptible from time a_2 until it becomes infected at event time t_p. The infection is detected at time d_1. Site f_{e_p} is infectious from time t_p until time s_p when the stock is slaughtered. Site f_q is active from time a_3 until the stock is slaughtered at time b. Since f_q is never infected in the study period, it remains susceptible from a_3 until b. (*b*) $I_{e_k e_p}(t) = 1$ for $t_k < t \leq t_p$, since in this time period site f_{e_k} could have infected site f_{e_p}. $I_{e_p e_k}(t)$ is never 1, i.e. site f_{e_p} could not have infected site f_{e_k}. $I_{e_k q}(t) = 1$ for $t_k < t \leq s_k$, because in this time period site f_{e_k} could in principle have infected site f_q, but site f_q did not become infected. $I_{e_p q}(t) = 1$ for $t_p < t \leq s_p$, since in this time period site f_{e_p} could in principle have infected site f_q, but site f_q did not become infected. $I_{q e_k}(t)$ and $I_{q e_p}(t)$ are never 1, since f_q is never infectious.

Table 2. Sizes of the local contact networks within municipalities that the farm sites active in 2002–2005 belong to. The percentages are given for all sites as well as separately for the ISA outbreak sites.

size of local contact network	sites with local contact network of this size (%)	outbreak sites with local contact network of this size (%)
no local contact network (1)	9	10
small (2–3)	46	41
medium (4–6)	34	39
large (7–9)	6	5
extra large (10–11)	5	5

monitored, for instance, the suppliers of smolt and the sharing of well boats.

The m sites that farm salmon at least some time during the study period are denoted by $f_1, \ldots, f_m$. Let n be the number of reported ISA infection events in this period. In our data $m = 1035$ and $n = 41$. The outbreak sites and their times of infection are $(f_{e_1}, t_1), \ldots, (f_{e_n}, t_n)$ such that $t_1 \leq t_2 \leq \ldots \leq t_n$, where $e_i \in \{1, \ldots, m\}$ and the time unit is day. The whole stock containing the ISA infected fish at site f_{e_i} is slaughtered at time $s_i \geq t_i$ (after the infection is detected). The site f_i has location x_i. The following definitions are illustrated in figure 2*a*.

Active site: A site is *active* at time t if it farms salmon at time t.

Event: An *event* at a site means that fish at that site become infected and that the infection disperses within the fish population at that site in such a way that (at a later time) ISA becomes detectable.

Detection time delay A: A is the detection time delay in months from an event until the infection is detected. In our study, it is fixed and deterministic, but two realistic values were compared.

ISA event time t_i: The time t_i is the time of the ith event; the ith ISA infection is detected at time $t_i + A$.

Infectious: ISA infected site f_{e_i} is *infectious* at time t for $t_i < t \leq s_i$, where s_i is the slaughtering time.

Susceptible: Site f_i is *susceptible* at time t if it is active and not infectious at time t.

The definitions of *detection time delay A* and *infectious* are simplifications. A comprise in fact two successive time periods; an unknown delay from event until the site becomes infectious and the period of infectiousness before the detection time. The pre-infectious period is presumably quite small compared to the latter, and is ignored here. Hence a site is infectious from the time point it becomes infected. Furthermore, A varies between cases and can only approximately be assumed as a constant. ISA has a rather long and variable incubation period. Reluctance of site managers to report ISA suspicion and different traditions at the various veterinary districts may also contribute to the variability in A. However, we keep A fixed, but experiment with two different values. Evidence from well boat movements of salmon smolts

Table 3. An overview of the covariates.

covariate	unit	description
t_i	day	day when site f_{e_i} became infected
$n_i(t)$	100 ton	biomass of fish at site f_i at time t
$d(x_j,x_i)$	km	seaway distance between sites f_j and f_i
k_{ji}	no unit	indicator which equals 1 when site f_j and site f_i are in the same local contact network, otherwise 0
$I_{ji}(t)$	no unit	indicator which equals 1 if site f_j is infectious and site f_i is susceptible at time t, otherwise 0
$J_i(t)$	no unit	indicator which equals 1 if site f_i is susceptible at time t, otherwise 0

Table 4. An overview of the parameters.

parameter	unit	factors
$\lambda_b(t)$	no unit	a time-varying risk of infection constant in space, i.e. shared by all farm sites. It is the baseline hazard, the log rate of transmission from site f_j to site f_i in the hypothetical setting $n_j(t)=n_i(t)=d(x_j,x_i)=k_{ji}=0$
α	$(100\ \text{ton})^{-1}$	the effect of increasing the biomass by 100 ton at an infectious farm site on the log rate of transmission to a susceptible farm site
β_1	$(100\ \text{ton})^{-1}$	the effect of increasing the biomass by 100 ton at a susceptible farm site on the log rate of transmission from an infectious farm site
ϕ	km^{-1}	the decrease in log rate of transmission from an infectious to a susceptible farm site caused by an increase of 1 km in the distance between them
γ	no unit	the increase in log rate of transmission from an infectious farm site to a susceptible farm site when the two farm sites are in the same local contact network, compared to when they are not
θ	no unit	the log rate of transmission to a susceptible farm site from sources other than infectious farm sites in the hypothetical setting that $n_i=0$
β_2	$(100\ \text{ton})^{-1}$	the effect of increasing the biomass by 100 ton at a susceptible farm site on the log rate of transmission from sources other than infectious farm sites
A	month	the detection time delay (not estimated)

in Scotland in 1998 suggest that the minimum incubation time from introduction of ISAV to the manifestation of clinical disease and mortality is roughly three months in a site (Stagg *et al.* 2001). A second line of evidence comes from the time period that salmon have been reared in seawater prior to ISA outbreaks. Epidemiological data compiled for 26 outbreaks of ISA in Norway during 2003–2005 gave a minimum rearing period of 6 months and a median period of 13 months in seawater prior to outbreak verification (T. M. Lyngstad 2006, National Veterinary Institute, personal communication). Given that the events occurred early in the seawater rearing phase in at least some of the outbreak sites, these observations indicate that the detection time delay A amounts to at least six months. We varied A between six and nine months for different runs of the model.

Let $\lambda_{ji}(t)$ be the rate of transmission from site f_j to site f_i at time t. Let $n_i(t)$ be the biomass of fish in 100 ton (ton = metric ton) at site f_i at time t, $d(x_j, x_i)$ is the seaway distance in kilometre between sites f_j and f_i and k_{ji} is an indicator which equals 1 when sites f_j and f_i are in the same local contact network. Furthermore, let

$$I_{ji}(t) = \begin{cases} 1 & \text{if site } f_j \text{ is infectious and site } f_i \text{ is susceptible at time } t, \\ 0 & \text{otherwise.} \end{cases} \tag{4.1}$$

We show $I_{ji}(t)$ for an illustrational example in figure 2*b*.

We model the rate of transmission from site f_j to site f_i at time t as

$$\lambda_{ji}(t) = \lambda_b(t)\exp\big(\alpha n_j(t) + \beta_1 n_i(t)\big)\cdot \big[\exp\big(-\phi d(x_j, x_i)\big) + k_{ji}\exp(\gamma)\big] I_{ji}(t).$$

This model assumes an exponential variation of the risk with seaway distance. Table 3 shows an overview of all the covariates with a description and their respective units. Table 4 shows an overview of all the parameters with units and explanations of their respective roles in the model.

To account for transmission pathways originating from unknown sources, we introduce a further term in the model. Let the rate of transmission $\lambda_{0i}(t)$ from sources other than farm sites to site f_i at time t be

$$\lambda_{0i}(t) = \lambda_b(t)\exp(\theta + \beta_2 n_i(t))J_i(t),$$

where $J_i(t)$ is an indicator which is 1 if site f_i is susceptible at time t. For example, infected salmon smolt and well boat effects can be captured in the parameters θ and β_2.

Following Keeling *et al.* (2001) and Diggle (2006), the intensity for an event at site f_i at time t is

$$\lambda_i(t) = \sum_{j=0}^{n} \lambda_{ji}(t). \tag{4.2}$$

In model (4.2), we sum up all the sources from which site f_i may have been infected, given the previous history; note that the '0' source is also included.

4.2. Fitting the model

Diggle (2006) proposes to estimate the parameters in (4.2) by partial likelihood. If there are no ties, the estimates of the parameters in (4.2) are obtained by maximizing the partial likelihood

$$\prod_{i=1}^{n} \frac{\lambda_{e_i}(t_i)}{\sum_{k\in\mathcal{R}_i}\lambda_k(t_i)}, \tag{4.3}$$

where $\mathcal{R}_t$ is the at-risk-set (of sites) at time t such that $k\in\mathcal{R}_t$ if site f_k is susceptible at time t. If ties occur, a modification of (4.3) is necessary. Let $t_1^*,\ldots,t_D^*$ be the distinct event times $(t_1^*<t_2^*\cdots<t_D^*)$, d_i the number of events at time t_i^* and e_i^* the set of events happening at time t_i^*. An approximation to the partial likelihood is (Efron 1977)

$$\prod_{i=1}^{D}\prod_{l=1}^{d_i}\frac{\lambda_{e_i^*(l)}(t_i^*)}{\sum_{k\in\mathcal{R}_i}\lambda_k(t_i^*)-\frac{l-1}{d_i}\sum_{h=1}^{d_i}\lambda_{e_i^*(h)}(t_i^*)}.$$

We used the Nelder–Mead optimization algorithm (Nelder & Mead 1965) implemented in the function *optim* in the statistical software *R* to maximize the partial likelihood. Parameter uncertainties are based on the observed Fisher information matrix (see, for example, Pawitan 2001).

As long as the baseline hazard $\lambda_b(t)$ is non-parametric, the partial likelihood is an equivalent version of the full likelihood with respect to the estimation of the parameters (Cox 1975). The efficiency gain by using a fully parametric baseline hazard and a full likelihood to give more precise results tends to be fairly small (Kalbfleisch & Prentice 2002).

5. RESULTS AND DISCUSSION

Estimated parameters for model (4.2) are given in table 5, together with estimated 95% confidence intervals. Two separate estimations were performed, one for the detection time delay $A=6$ months and another for $A=9$ months.

At a 5% confidence level, the distance parameter ϕ is significantly positive for both values of A. Hence, the risk of a susceptible site becoming infected by an infectious site decreases with increasing seaway distance between the sites. Of particular interest is the relative importance of the distance parameter ϕ and the local contact network parameter, γ. The smaller the γ, the lesser the effect of local contact network. The risk implied by a distance of 0 km from an infectious farm is more than seven times the risk caused by being in the same local contact network as an infectious farm. Being in the same local contact network as a farm site with an ISA outbreak has the same effect as being at a seaway distance of $-\gamma/\phi$ km from a site with an ISA outbreak and $-\gamma/\phi=5$ for both values of detection time delay parameter A (six and nine months). This means that having an infectious site at a seaway distance between 0 and 5 km implies more risk of being infected than being in the same local contact network as an infectious site. Our results are based on the exponential decay of the effect of distance on the rate of transmission $\lambda_{ji}(t)$, which is a natural assumption (starting with Cox 1975 and including Diggle 2006). The decay is necessarily sublinear, but other functions could be assumed, possibly leading to different results.

Table 5. Parameter estimates with corresponding estimated confidence intervals.

A	parameter	estimate	95% confidence interval
6	α	0.127	(0.020, 0.234)
	β_1	0.102	(−0.015, 0.220)
	ϕ	0.415	(0.051, 0.780)
	γ	−2.013	(−4.711, 0.685)
	θ	−2.263	(−4.416, −0.381)
	β_2	0.019	(−0.039, 0.077)
9	α	0.378	(0.190, 0.567)
	β_1	−0.041	(−0.239, 0.156)
	ϕ	1.273	(0.600, 1.946)
	γ	−6.083	(−9.531, −2.634)
	θ	−3.410	(−5.099, −1.720)
	β_2	0.001	(−0.061, 0.064)

Before the study, we suspected that susceptibility would increase with increasing biomass at the susceptible farm, i.e. β_1 and β_2 would be positive. Hammell & Dohoo (2005) looked at fish density and found that a low fish density in cages reduces the ISA susceptibility. Although biomass is not the same as density, it may capture the same risk factor. Our results for β_1 and β_2 show no clear effects of biomass on susceptibility. These parameters are not significantly different from 0 for neither values of the detection time delay parameter A (six or nine months). We also suspected that infectiousness would increase with increasing biomass at the infectious site. The parameter α is significantly positive for both $A=6$ and 9 months indicating that of two infectious farm sites, the site with the most biomass is the most infectious. The sign of θ is not of particular interest. $\exp(\theta)$ is the constant rate of transmission to a susceptible farm site from sources other than the infectious farm sites.

It is of interest to quantify the fraction of total risk explained by seaway distance to infectious farm sites, being in the same local contact network as infectious farm sites and sources other than infectious farm sites. For this purpose, we introduce the fraction of total risk explained by seaway distance

$$r_{\text{distance}}=\frac{\lambda_b(t)\sum_{i=1}^{m}\sum_{t\in T_i}\sum_{j\in U_t}\exp(\alpha n_j(t)+\beta_1 n_i(t))\exp(-\phi d(x_j,x_i))I_{ji}(t)}{\sum_{i=1}^{m}\sum_{t\in T_i}\sum_{j\in U_t}\lambda_{ji}(t)},$$

the fraction of total risk explained by local contact network

$$r_{\text{network}}=\frac{\lambda_b(t)\sum_{i=1}^{m}\sum_{t\in T_i}\sum_{j\in U_t}\exp(\alpha n_j(t)+\beta_1 n_i(t))k_{ji}\exp(\gamma)I_{ji}(t)}{\sum_{i=1}^{m}\sum_{t\in T_i}\sum_{j\in U_t}\lambda_{ji}(t)},$$

and the fraction of total risk explained by other sources

$$r_0=\frac{\sum_{i=1}^{m}\sum_{t\in T_i}\lambda_{0i}(t)}{\sum_{i=1}^{m}\sum_{t\in T_i}\sum_{j\in U_t}\lambda_{ji}(t)}.$$

Here, $m=1035$ is the total number of sites, T_i is the set of days when site f_i is susceptible during the study period and U_t is the set of sites which are infectious at time t, including the '0' source.

The quantities r_{distance}, r_{network} and r_0 are estimated by plugging in the parameter estimates. The results can be seen in table 6. We see that r_0 indicate that roughly

Table 6. Estimated fractions of total risk explained by the seaway distance to infectious farm sites ($\hat{r}_{\text{distance}}$), by being in the same local contact network as infectious farm sites ($\hat{r}_{\text{network}}$) or by sources other than infectious farm sites ($\hat{r}_0$).

	A	
	6	9
$\hat{r}_{\text{distance}}$	0.135	0.141
$\hat{r}_{\text{network}}$	0.099	0.171
$\hat{r}_0$	0.766	0.687

70% of the total risk is explained by sources other than direct transmission from infectious farm sites. Seaway distance and local contact networks explain roughly the same fraction of the total risk.

Recall that common ownership within a municipality is used as the local contact network variable. This may not represent the local contact network accurately enough. In this sense, the local contact network effect may be underestimated. Similarly, the effect of seaway distance may be underestimated. The effective distance between two sites can be a rather complex function of seaway distance and local tidal hydrodynamics (Chang *et al.* 2005). Our simplified assumption might lead to a bias towards zero estimate of the distance parameter ϕ.

The denominator in r_{distance}, r_{network} and r_0 summarizes the total risk from all sources over all sites over the whole period, while the numerator summarizes the total risk explained by the seaway distance to infectious farm sites (r_{distance}), being in the same local contact network as infectious farm sites (r_{network}) or some other sources than infectious farm sites (r_0). They therefore include sites that are at infinite distance from infectious farm sites, where the only possible risk is from other sources.

We also analysed the dataset including the under-reported years 2000 and 2001. The results were quite similar to the results previously shown, but they were less conclusive. Inference on the detection time delay parameter A from present data is hard, because it is nearly unidentifiable, confounding with several other parameters.

6. CONCLUSIONS

We have developed a stochastic model to quantify individual risk factors in the transmission of ISA in salmon farming. Seaway distance and local contact networks are found to be factors which affect the transmission between sites, and they explain roughly the same amount of the total risk. Although these factors can be underestimated, there is strong evidence that there is a large component of the total risk caused by some other sources than transmission of the virus from infectious sites. Being in the same local contact network as an ISA event site has the same effect as being at a seaway distance of 5 km from an ISA event site. This means that there is more risk involved in having an infectious site at a seaway distance from 0 to 5 km than being in the same local contact network as an infectious site. This supports a policy which requires a minimum distance between sites, but it also means that placing two sites considerably more than 5 km apart for the purpose of minimizing the risk of ISA dispersing from one to the other is of little value if the two sites are in the same local contact network. There is evidence that biomass influences infectiousness of farms. However, the model did not detect clear effects of biomass on susceptibility. The relatively small number of ISA cases in our dataset limits the precision in our results. Furthermore, the results show that more data is needed in order to identify the transmission risk factors incorporated into $\lambda_{0i}(t)$, that is transmission from sources other than infected farm sites. For example, data on well boat traffic and smolt suppliers would help to explain $\lambda_{0i}(t)$. Our study highlights the need to monitor putative pathways for ISAV infection to better control the spread of ISA, such as ISAV incidence and dispersal patterns for smolt from freshwater to seawater sites and well boat traffic. Our approach can be applied further to other diseases and processes, in order to detangle basic anthropogenic factors, such as ownership networks, from natural ones. In particular, if appropriate data were available, one could study emerging diseases that impose constraints on a vigorous development of aquaculture (Murray & Peeler 2005).

This work was partly funded by the Research Council of Norway, P.A.J. grant no 152029 and project 154079/420. We are grateful to Knut Johan Johnsen, the Directorate of Fisheries, Bergen, Norway, for providing the data on salmon biomass and to three anonymous referees.

REFERENCES

Bouchard, D. A., Brockway, K., Giray, C., Keleher, W. & Merrill, P. L. 2001 First report of infectious salmon anaemia (ISA) in the United States. *Bull. Eur. Assoc. Fish Pathol.* **21**, 86–88.

Chang, B. D., Page, F. H., Losier, R. J., Greenberg, D. A., Chaffey, J. D. & McCurdy, E. P. 2005 Application of a tidal circulation model for fish health management of salmon farms in the Grand Manan Island area, Bay of Fundy. *Bull. Aquac. Assoc. Can.* **105-1**, 22–33.

Cox, D. R. 1975 Partial likelihood. *Biometrika* **62**, 269–276. (doi:10.1093/biomet/62.2.269)

Diggle, P. J. 2006 Spatio-temporal point processes, partial likelihood, foot and mouth disease. *Stat. Methods Med. Res.* **15**, 325–336. (doi:10.1191/0962280206sm454oa)

Efron, B. 1977 The efficiency of Cox's likelihood function for censored data. *J. Am. Stat. Assoc.* **72**, 557–565. (doi:10.2307/2286217)

Gustafson, L. L., Ellis, S. K. & Bartlett, C. A. 2005 Using expert opinion to identify risk factors important to infectious salmon-anemia (ISA) outbreaks on salmon farms in Maine, USA and New Brunswick, Canada. *Prev. Vet. Med.* **70**, 17–28. (doi:10.1016/j.prevetmed.2005.02.012)

Hammell, K. L. & Dohoo, I. R. 2005 Risk factors associated with mortalities attributed to infectious salmon anaemia virus in New Brunswick, Canada. *J. Fish Dis.* **28**, 651–661. (doi:10.1111/j.1365-2761.2005.00668.x)

Jarp, J. & Karlsen, E. 1997 Infectious salmon anaemia (ISA) risk factors in sea-cultured Atlantic salmon *Salmo salar*. *Dis. Aquat. Org.* **28**, 79–86.

Kalbfleisch, J. D. & Prentice, R. L. 2002 *The statistical analysis of failure time data*, ch. 5.9, 2nd edn. New York, NY: Wiley.

Keeling, M. J. *et al.* 2001 Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* **294**, 813–817. (doi:10.1126/science.1065973)

Kibenge, F. S. B., Garate, O. N., Johnson, G., Arriagada, R., Kibenge, M. J. T. & Wadowska, D. 2001 Isolation and identification of infectious salmon anaemia virus (ISAV) from Coho salmon in Chile. *Dis. Aquat. Org.* **45**, 9–18.

Krossøy, B., Hordvik, I., Nilsen, F., Nylund, A. & Endresen, C. 1999 The putative polymerase sequence of infectious salmon anemia virus suggests a new genus within the Orthomyxoviridae. *J. Virol.* **73**, 2136–2142.

Kvellestad, A., Bornø, G., Flesjå, K. I., Nilsen, H., Skjelstad, H. & Hjeltnes, B. 2005 Helsesituasjonen hos laksefisk. In *Kyst og Havbruk 2005*, vol. 2 (eds K. Boxaspen, A.-L. Agnalt, J. Gjøsæter, L. L. Jørgensen & A. B. Skiftesvik) Fisken og Havet, særnummer, pp. 97–101. Bergen, Norway: Havforskningsinstituttet.

Løvdal, T. & Enger, Ø. 2002 Detection of infectious salmon anemia virus in sea water by nested RT-PCR. *Dis. Aquat. Org.* **49**, 123–128.

Lyngøy, C. 2003 Infectious salmon anemia in Norway and the Faroe Islands: an industrial approach. In *International response to infectious salmon anaemia: prevention, control and eradication* (eds O. Miller & R. Cipriano), pp. 97–109. Washington, DC: US Department of Agriculture.

McClure, C. A., Hammell, K. L. & Dohoo, I. R. 2005 Risk factors for outbreaks of infectious salmon anemia in farmed Atlantic salmon. *Salmo salar. Prev. Vet. Med.* **72**, 263–280. (doi:10.1016/j.prevetmed.2005.07.010)

Mullins, J. E., Groman, D. & Wadowska, D. 1998 Infectious salmon anaemia in salt water Atlantic salmon (*Salmo salar* L.) in New Brunswick, Canada. *Bull. Eur. Assoc. Fish Pathol.* **18**, 110–114.

Munro, P. D., Murray, A. G., Fraser, D. I. & Peeler, J. 2003 An evaluation of the risk of infectious salmon anaemia transmission associated with different salmon harvesting methods in Scotland. *Ocean Coast. Manage.* **46**, 157–174. (doi:10.1016/S0964-5691(02)00125-4)

Murray, A. G. 2006 A model of the emergence of infectious pancreatic necrosis virus in Scottish salmon farms 1996–2003. *Ecol. Model.* **199**, 64–72. (doi:10.1016/j.ecolmodel.2006.06.010)

Murray, A. G. & Peeler, E. J. 2005 A framework for understanding the potential for emerging diseases in aquaculture. *Prev. Med. Vet.* **67**, 223–235. (doi:10.1016/j.prevetmed.2004.10.012)

Murray, A. G., Smith, R. J. & Stagg, R. M. 2002 Shipping and the spread of infectious salmon anemia in Scottish aquaculture. *Emerg. Infect. Dis.* **8**, 1–5.

Nelder, J. A. & Mead, R. 1965 A simplex algorithm for function minimisation. *Comput. J.* **7**, 308–313.

Nylund, A., Alexandersen, S., Rolland, J. B. & Jacobsen, P. 1995 Infectious salmon anemia virus (ISAV) in brown trout. *J. Aquat. Anim. Health* **7**, 236–240. (doi:10.1577/1548-8667(1995)007<0236:ISAVII>2.3.CO;2)

Nylund, A., Plarre, H., Karlsen, M., Fridell, F., Ottem, K. F., Bratland, A. & Sæther, P. A. 2007 Transmission of infectious salmon anaemia virus (ISAV) in farmed populations of Atlantic salmon (*Salmo salar*). *Arch. Virol.* **152**, 151–179. (doi:10.1007/s00705-006-0825-9)

Pawitan, Y. 2001 *In all likelihood—statistical modelling and inference using likelihood.* Oxford, UK: Clarendon Press.

Plarre, H., Devold, M., Snow, M. & Nylund, A. 2005 Prevalence of infectious salmon anaemia virus (ISAV) in wild salmonids in western Norway. *Dis. Aquat. Org.* **66**, 71–79.

Rodger, H. D., Turnbull, T., Muir, F., Millar, S. & Richards, R. H. 1998 Infectious salmon anaemia (ISA) in the United Kingdom. *Bull. Eur. Assoc. Fish Pathol.* **18**, 115–116.

Sharkey, K. J., Fernandez, C., Morgan, K. L., Peeler, E., Thrush, M., Turnbull, J. F. & Bowers, R. G. 2006 Pair-level approximations to the spatio-temporal dynamics of epidemics on asymmetric contact networks. *J. Math. Biol.* **53**, 61–85. (doi:10.1007/s00285-006-0377-3)

Snow, M., Raynard, R. S. & Bruno, D. W. 2001 Comparative susceptibility of Arctic char (*Salvelinus alpinus*), rainbow trout (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*) to the Scottish isolate of infectious salmon anaemia virus. *Aquaculture* **196**, 47–54. (doi:10.1016/S0044-8486(00)00588-3)

Stagg, R. M. *et al.* 2001 Epizootiological investigations into an outbreak of infectious salmon anemia (ISA) in Scotland, FRS Marine Laboratory Report 13/01, p. 60. Aberdeen, UK.

Statistics-Norway 2006 Fish farming: salmon setting all-time high, http://www.ssb.no/english/subjects/10/05/.

Thorud, K. 1991 Infectious salmon anaemia: transmission trials, haematological, clinical, chemical and morphological investigations, Ph.D. thesis, Norwegian College of Veterinary Medicine, Oslo, Norway.

Thorud, K. & Djupvik, H. O. 1988 Infectious salmon anaemia in Atlantic salmon (*Salmo salar* L.). *Bull. Eur. Assoc. Fish Pathol.* **8**, 109–111.

Thorud, K. & Håstein, T. 2003 Experiences with regulatory responses to infectious salmon anaemia in Norway. In *International response to infectious salmon anaemia: prevention, control and eradication* (eds O. Miller & R. C. Cipriano), pp. 155–159. Washington, DC: US Department of Agriculture.

Thrush, M. & Peeler, E. J. 2006 Stochastic simulation of live salmonid movement in England and Wales to predict potential spread of exotic pathogens. *Dis. Aquat. Org.* **72**, 115–123.

Vågsholm, I., Djupvik, H. O., Willumsen, F. V., Tveit, A. M. & Tangen, K. 1994 Infectious salmon anaemia (ISA) epidemiology in Norway. *Prev. Vet. Med.* **19**, 277–290. (doi:10.1016/0167-5877(94)90095-7)