An Epidemiological Model Of A Pathogen Affecting Aquaculture: Infectious Pancreatic Necrosis Virus In Scottish Farmed Salmon

[1]**Murray, A.G.**

[1]FRS Marine Laboratory, Aberdeen, UK E-Mail: **murrays@marlab.ac.uk**

EXTENDED ABSTRACT

Aquacultural production has increased rapidly over the last few decades, however several diseases have emerged that have impeded this rise. For example, Infectious Pancreatic Necrosis virus (IPNV) affects farmed salmonids in many countries. In the UK, until 2005, attempts were made to control the virus in salmon by imposing movement restrictions on infected sites and by testing parent stock to prevent vertical transmission to eggs.

Data to implement this control policy in Scotland were collected by Fisheries Research Services Fish Health Inspectors. I have used this data to obtain national and regional patterns in the prevalence of IPNV in salmon farms; strong increases occurred from 1996-2003 in both marine (30-80%+) and freshwater (5-33%) sites, with considerable regional variation in trends.

The FHI data have also been used to analyse dynamics of infection by looking at patterns in the probability of persistence of the virus on sites. Infection appears to have been rather short lived with the probability of a site being infected after 2 years independent of initial infection status, and to strike sites stochastically. This may be due to the fallowing of sites after an 18 month production cycle. High turnover and the high prevalence implies a rapid spread of infection.

Using the results above, a simple susceptible-infected (SI) model was developed of IPNV epidemiology in both freshwater and marine salmon farms (Fig 1). Fish are held in freshwater for 1 year and at sea for 18 months and can become infected in either environment. If any of the freshwater smolts delivered to a marine site are infected then that site is infected. Once a population is infected it is assumed to remain so until harvested; but, after fallowing, IPNV does not persist in environmental reservoirs. Scottish salmon production increased substantially over the period modelled, so results from density independent, and density dependent models are compared.

This simple model gives a good fit to different regional patterns of emergence with similar regional parameter values, implying similar processes occur in the different regions. Density dependent versions of the model fit observations slightly better than density independent versions. The model indicates IPNV prevalence would probably stabilise at 90% of marine sites and 40-50% of freshwater sites if control policies were unchanged.
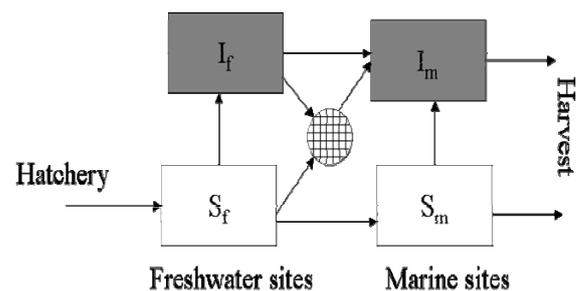
Figure 1. Structure of IPNV infection model S =uninfected susceptible, I = infected; subscripts f = freshwater, m =marine.

The model has significant implications for the management of IPNV. Improved control of transmission in freshwater is the most effective way of reducing infection, even in marine waters, but eradication would require substantial improvements in both marine and freshwater controls and also in sampling frequency. Such increased effort is unlikely to be cost-effective and official controls are being reduced and replaced with industry-based controls. An area, rather than site-level, approach to IPNV management might be more effective, when combined with husbandry measures to limit clinical disease in infected sites.

1. INTRODUCTION

Aquaculture has grown rapidly in recent decades. However, for reasons described by Murray and Peeler (2005) this increasing production has been inhibited by the emergence of diseases. Some diseases have undermined entire sectors, for example QX (*Marteilia sydneyi*) in New South Wales oyster fisheries.

Modelling has been used to simulate the spread of disease among human and other animal populations for many decades (Anderson and May 1979). However its application to aquatic environments has been more restricted. Models of large-scale spread in Australian pilchards (Murray et al. 2003a) and North Sea seals (Swinton et al. 1998) have looked at spread of disease through wild populations, but in aquaculture modelling has largely been restricted to general principles (Reno 1998) or to modelling spread within individual populations e.g. White Spot Syndrome in Shrimp farms (Lotz and Soto 2002) and Infectious Pancreatic Necrosis (Smith et al. 2000) in experimental tank populations.

In this paper I take data from an official surveillance program that continued up to 2005 to develop a model of the spread of a pathogen among hundreds of sites throughout a country (FRS 2003). The disease is infectious pancreatic necrosis (IPN), considered the most economically damaging viral infection of farmed salmon in the EU (Ariel and Olensen 2002).

2. DETERMINING PATTERNS IN PREVALENCE OF IPNV INFECTION

Data on the presence/absence of IPNV infection have been collected from all salmon farming sites for many years by Fish Health Inspectors (FHI) to support control policies (FRS 2003). Positive tests resulted in movement controls measures and other financial costs. Because of their significance, test results have been subject to close scrutiny and are therefore highly reliable. Although testing effort may vary between years, regions and seasons, calculating prevalence, rather than numbers of, positive tests discount for this variation in effort. Therefore prevalence, the proportion of positive test results has been used as the standard measure of IPNV infection.

Note that throughout this paper all data, both observations and model results, refer to the presence of infection, not disease. Most infected sites do not have clinical IPN disease (Murray et al. 2004).

Both national and regional prevalence have been calculated for marine and freshwaters (Murray et al. 2003b). Regions have been defined on the basis of the United Kingdom Ordnance Survey's 100 km grid squares. Five regions are used (Fig. 2): Shetland, Orkney, the Western Isles and northern and southern mainland (separated by the 800 km north line).

In this paper I model the changing prevalence of infection in fish as they develop from fry to mature salmon, however freshwater sites also include adult broodstock salmon, which are not part of the model. We have therefore excluded broodstock sites from the data analysed.
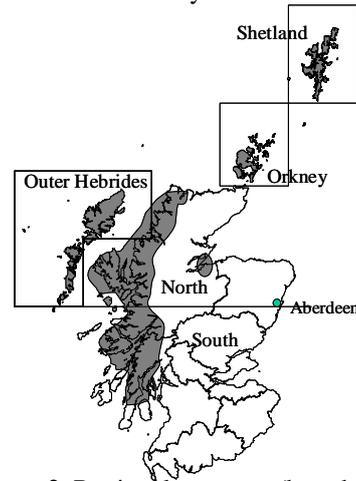

Figure 2. Regional structure (based on 100 km squares) of IPNV analysis. Marine salmon farming areas shaded.

In each region and for each year of 1996-2003 the local mean prevalence of IPNV has been calculated as the proportion of samples that was positive. Prevalence has been calculated separately for freshwater and marine environments. However seasonal differences have been shown not to contribute significantly to variation (Murray et al. 2003b).
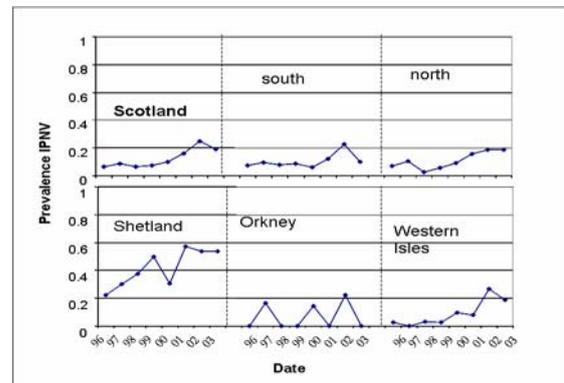

Figure 3. IPNV prevalence in freshwater salmon farms 1996-2003, nationally and by regions.

Prevalence in freshwater has increased throughout the period 1996-2003, and particularly from 2000. In most regions the increase has been from about 5% to 20%, but in Shetland the increase has been from 20% to 60% (Fig. 3). In 2003 the increase shows signs of slowing. Only 4 positive samples were obtained from Orkney, once broodstock sites were removed. This is insufficient data to constrain trends, although it does show prevalence was low.
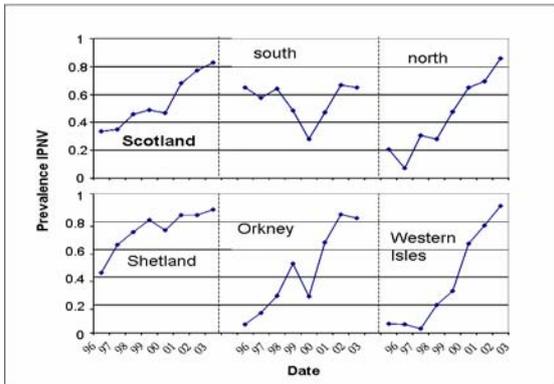

Figure 4. IPNV prevalence in marine salmon farms 1996-2003, nationally and by regions.

Prevalence of IPNV in marine sites has been higher and increased faster than in freshwater, so that by 2003 high prevalence occurred everywhere (Fig. 4). However, each region showed a different pattern of increase, except northern Scotland and Orkney which both showed a linear increase from low to high levels. Shetland reached 890% prevalence by 1999 and increase slowed, while IPNV prevalence in the Western Isles was very low until 1999, but thereafter increased rapidly. In the south IPNV prevalence showed little trend. All regions showed a lower than expected value in 2000, probably reflecting control measure taken against another disease epidemic in 1998-9.

3. PERSISTANCE OF INFECTION

IPNV infection might persist for prolonged periods or repeatedly infect certain sites, alternatively it might persist for only short periods and infect sites at random. The pattern will be reflected in changes in conditional probability, the probability of obtaining a positive sample given that a sample taken at some earlier time was positive or was negative. If IPNV is persistent, or infects some sites repeatedly, then the conditional probabilities the site will be infected will be different for sites that earlier returned positive and negative samples even after prolonged periods (Fig. 5). Conversely if infection does not persist but affects sites at random, then the probability of infection will (after

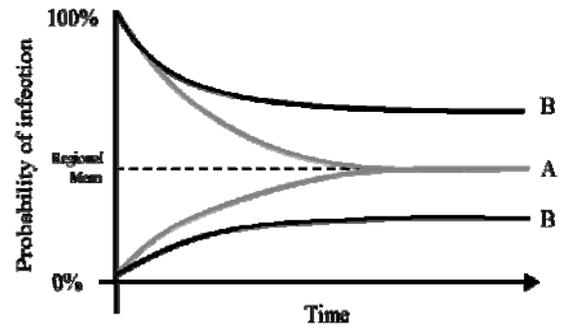sufficient time) become independent of whether earlier samples were positive or negative.

Figure 5. Conditional probability of infection with time between measurements. Theory A. conditional probabilities converge; theory B. conditional probabilities remain distinct.

Marine conditional probabilities of infection appear to show incomplete convergence, even after 4 years an initially infected site is more likely to be infected than an initially uninfected site. However with major regional differences in prevalence probabilities of infection of initial and second samples are associated at the regional level. If the data are analysed on a regional basis then conditional probabilities do converge after about 2 years. The southern mainland region is used to illustrate convergence (Fig. 6) because, with constant moderately high levels of infection (Fig. 4) it is possible to get long-term data on both initially positive and initially negative sites, but similar patterns do apply elsewhere. Two years is about the length of time salmon are kept at sea before they are harvested and the site fallowed. The regional convergence in conditional probabilities suggests infection does not survive fallowing and that sites are not re-infected at higher probability than others (other than at the regional level).
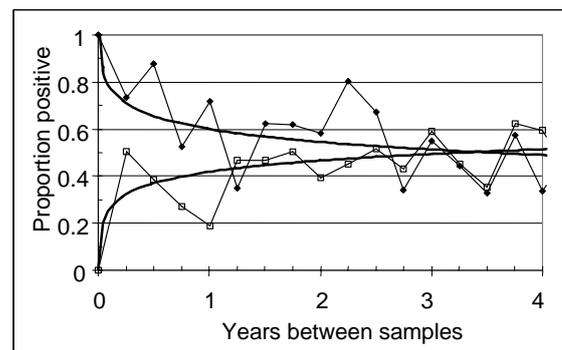

Figure 6. Observed conditional probabilities of infection in second samples for marine farms in the southern mainland region by quarters. Mean values and regression with log time shown. Lower lines if initially negative, upper lines if initially positive (see Fig. 5).

For freshwater sites conditional probabilities do not converge completely even at 4 years, either nationally or when Shetland (the only region with a different prevalence history, Fig. 3) is removed (not shown). A small number of sites have been repeatedly found to be infected. However, conditional probabilities do converge substantially in the first year or so, therefore many sites do change infection status in a relatively short period.

In conclusion conditional probabilities show rapid convergence over one to two years, implying that infection status changes rapidly. In marine sites infection history appears completely irrelevant after about 2 years, implying infection rarely persisted after sites were fallowed and infection occurred at random. A rapid change in infection status also applies in freshwater sites, again implying mostly short-lived infection, however in a few sites infection persists or recurs for long periods. With short lived infection, high observed prevalence implies rapid transmission.

4. EPIDEMIOLOGICAL MODELLING

The data collected by FHI on IPNV have allowed us to obtain considerable information on patterns in the prevalence and dynamics of the infection. This information allows the development and testing of an epidemiological model of the emergence of the virus from relatively low levels in 1996 to near ubiquity by 2003.

The modelling approach is a susceptible–infected model (Anderson and May 1979) in which the population is divided into farms that are infected (I) and susceptible (S) farms that are uninfected (shown earlier in Fig. 1). These farms are divided into freshwater and marine farms. Because of extensive testing for IPNV and destruction of eggs from infected parents, it is assumed that fry are initially uninfected. They are held for 1 year in freshwater, where they may become infected, before being moved to marine sites. Marine sites that receive infected fish (now called smolts) become infected; marine sites may receive smolts from more than 1 freshwater sites, increasing the risk of infection. The fish are then held for 1 year in the marine sites before being harvested, at which time the site is cleared and fallowed so infection does not persist (in line with observed conditional probabilities, Fig. 6). Separate runs of the model are carried out with national and regional data to allow regional variation to be explored.

Transmission of infection is proportional to the product of infected and susceptible farms (after Anderson and May 1979). Two forms of this relationship are used: a density independent form, based on the proportions of farms infected and susceptible, and a density dependent form that takes account of the increased production to estimate the total populations in infected and uninfected farms.

The equations for IPNV transmission in freshwater are:

(1) $\qquad dS_f/dt = s - m_y b_f S_f I_f - s S_f$

(2) $\qquad dI_f/dt = m_y b_f S_f I_f - s I_f$

Here S_f is the proportion of freshwater farms that are susceptible to infection and I_f the proportion that are infected. The rate of input of fry is $s = 1$ year^{-1}, b_f is the infection transmission coefficient in freshwater and m_y is population relative to 1996.

The equations for transmission between marine sites are:

(3) $\qquad dS_m/dt = hX - m_y b_m S_m I_m - h S_m$

(4) $\qquad dI_m/dt = h(1 - X) + m_y b_m S_m I_m - h I_m$

Here S_m and I_m are the proportions of marine populations that are susceptible and infected. The marine transmission coefficient is b_m and m_y is the population level. The proportional rate of input is $h = 2/3$ year^{-1} and X is the proportion of inputs that include no fish from infected freshwater farms.

The value of X depends on the number of sources of smolts, k, and the proportion of freshwater sites that are infected I_f:

(5) $\qquad X = I_f k/(1 + I_f(k-1))$

The production of salmon in Scotland nearly doubled over the period 1996-2002 from 20 to 34 million fish year^{-1} (Stagg and Smith 2003). The use of normalised data allows production to be used as a proxy for population assuming the relationship between these variables has not changed. Therefore a function to describe the increased biomass of fish relative to 1996 levels was used:

(6) $\qquad m_y = 1 + P \times \ln(\text{Year} - 1995)$

The parameter P was fitted to observed production, both at the national level and for the different regions. The logarithmic nature of the function reflects the maturation of the industry and the lack of suitable new sites for farming.

Fitting was achieved by minimising root mean square difference between observations and model

results. First the value of P was fitted to production data. Then freshwater IPNV prevalence was fitted before fitting marine IPNV. The freshwater IPNV prevalence depends only on b_f and the initial value of I_f as other parameters and salmon production are fixed. Marine IPNV depends on freshwater IPNV as well as on b_m and I_m and is therefore fitted only once the freshwater IPNV is fitted.
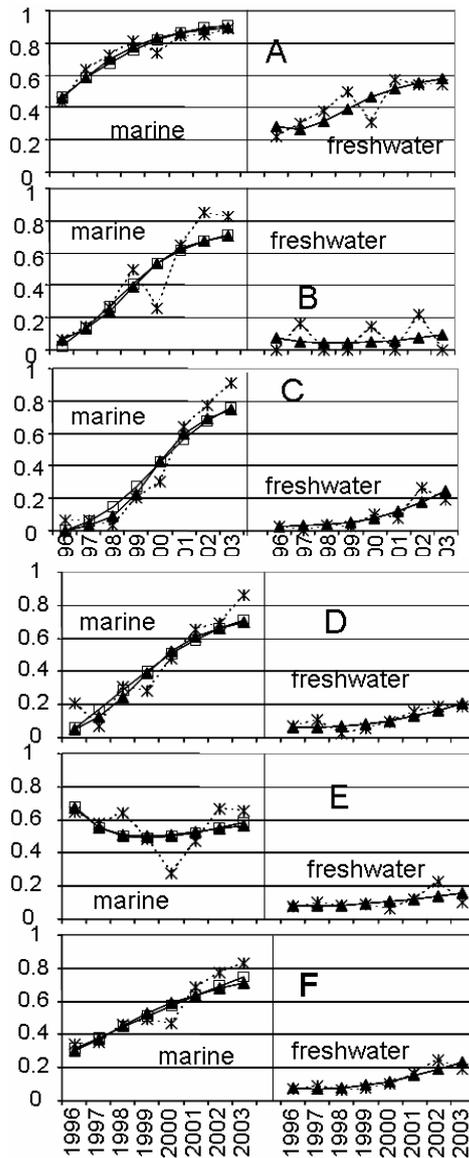
5. RESULTS

Figure 7. Density dependent model simulations by region. 3-M (solid triangles) and 1-M (hollow squares) give nearly identical fits (identical in freshwater, so squares not shown) to observations (stars). A = Shetland, B = Orkney, C = Western Isles, D = northern mainland, E = southern mainland, **F** = all Scotland.

The model has been fitted to observation, as described above. Both density independent and density dependent models fitted observations well in spite of considerable differences in regional patterns. Results from the density dependent modelling were slightly better than density independent and are shown in Fig. 7. In particular density dependent modelling can describe initially low and slowly increasing prevalence and later much higher values.

Model simulations assuming 1 or 3 freshwater sources of smolts per marine site provide a similarly good fit. However observations typically show 2 or 3 sources of smolts per marine site (Murray et al. 2004). Comparison of simulated transmission rates required to fit simulations with 1 and 3 sources can be used to assess the relative contributions to IPNV prevalence of the use of multiple smolt sources and that due to transmission within the marine environment

One of the most useful statistics in epidemiology is the increase ratio R_0, (see Reno 1998 for discussion) this is the number of new infections created per existing infection before this initial infection is removed, assuming there is no infection in the rest of the population. Only if $R_0 < 1$ in both fresh and marine water will the virus be eradicated (although at low R_0 and low prevalence stochastic eradication is possible). This value is equivalent to $b_f m_y/s$ or $b_m m_y/h$ for fresh and marine waters. Note that under density dependent transmission the value of R_0 increases with population density.

Table 1. Increase ratios (R_0) required to fit observed Scottish IPNV prevalence in freshwater and in marine waters with k =3 (M-3) or k = 1 (M-1). DD = density dependent, DI = density independent.

	M-3	M-1	Fresh
DD min	0.98	1.40	0.86
DD max	1.77	2.55	1.57
DD mean	1.48	2.14	1.31
DI	1.45	2.13	1.41

R_0 values have been calculated for Scotland (Table 1) and at the regional levels (not shown). In the DI model, and the average for the DD model, transmission in both marine (M-3) and freshwaters generates an R_0 of around 1.4, indicating transmission would have to be cut by nearly a third in both environments to eradicate IPNV. However, increase in population means that in the density dependent model R0 increases through the

simulation and as a result approaches about 1.8 by the end of the simulation indicating even larger (45%) cuts in transmission may be required.

Transmission in marine waters is augmented by the use of multiple smolt sources. In the M-3 model R_0 only accounts for within seawater transmission, while in the M-1 model R_0 effectively combines the seawater spread and the (unmodelled) use of multiple smolt sources. This results in an increase of R_0 from 1.48 to 2.14. About 30% of this total transmission (2.14) is due to the use of multiple sources.

Table 2. Mean regional density dependent R_0 values. The k effect is % contribution of multiple smolt sources to total infection pressure (M-1).

Region	M-3	M-1	k effect	Fresh
Shetland	1.10	2.69	59%	1.93
Orkney	1.99	2.40	17%	1.08
Western Isles	1.72	2.50	31%	1.44
North	1.47	2.19	32%	1.29
South	1.03	1.64	37%	1.21

The model fits the different regional patterns with similar parameter values and hence similar regional R_0 (Table 2), indicating similar local epidemiological processes. The M-3 model indicates 30-40% of total local infection risk (M-1) to marine sites is due to multiple sources of smolts (not accounted for by M-3); the result under M-2 is about 20%. The southern region is an exception with R_0 much lower than elsewhere. As prevalence has been high for a long period, controls may be more established than in other regions. For Orkney, a lower rate of increase in freshwater and a lower contribution to marine infection pressure from multiple smolt sources probably is due to poor estimation by the model owing to the lack of freshwater data. Shetland also appears different with a much lower R_0 M-3 and high smolt contribution to infection risk, but this is deceptive. R_0 M-1 similar to other regions. Since Shetland imports many smolts from other regions, the true IPNV prevalence in smolts will be lower than the value this simple region-by-region modelling generates. Hence the modelled contribution of smolts to infection pressure is probably exaggerated.

R_0 can also be reduced by removing infected populations. Such culling is used to keep Sweden IPNV free (Ariel and Olensen 2002). However, at the high prevalence that exists in Scotland culling would be impractical.

If we assume similar transmission and production increase processes will occur in future we can project the model to estimate likely future prevalence of IPNV (Fig. 8).
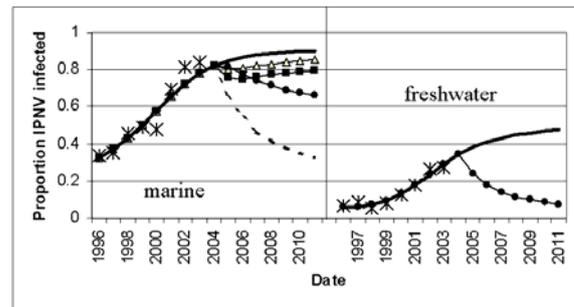

Figure 8. Projected density dependent prevalence of IPNV assuming no change (thick line) 50% cut in b_f (solid circles), 50% cut in b_m (open triangles) restriction to k = 1 (solid squares) combination of controls (dashed line). Star = observed values.

Prevalence, even allowing for likely increases in salmon production, is projected by the model to stabilise at levels only a little higher than current prevalence: 90% of marine sites and 40-50% of freshwater sites. Perhaps surprisingly, the most effective means of reducing IPNV prevalence in marine water would appear to be to reduce transmission in freshwater, b_f, by 50% (this is the only control predicted to reduce freshwater prevalence). Controls leading to 50% reduction in marine transmission b_m or restrictions on the number of sources of smolts, k, from 3 to 1 are rather ineffective. The largest reductions in IPNV prevalence are predicted when these controls are combined with controls on freshwater transmission as the different controls interact synergistically. It is also likely that, because of diminishing returns, it would be more cost effective to tighten controls moderately in several areas than strongly in a single area.

6. CONCLUSIONS

The aim of developing the IPNV epidemiological model was to explain the observed increasing prevalence of IPNV and to evaluate potential controls of IPNV prevalence. The modelling indicates co-coordinated control of multiple aspects of the spread of the virus is likely to be more effective than control of any one aspect, but that control in freshwater is the single most effective component.

Policies applied in the period upto 2005 have not prevented an increase in IPNV prevalence. The

effort required to eradicate IPNV is shown to be substantial and so is unlikely to be cost-effective. Ineffective controls mean that other countries' IPNV status cannot be taken into account for the purpose of trade in salmonids. With imports deregulated, internal movement controls became pointless and have ceased to be enforced. Also, this analysis indicates that site infection status changes quite rapidly. Therefore, sampling at 1 to 2 year intervals is too infrequent for movement controls to be effective. This does not apply to sampling for control of vertical transmission. Industry based husbandry methods to reduce the risk of clinical disease may be more appropriate than official controls on the virus (Murray et al. 2004).

The model describes epidemic spread between farms at the large-scale, as opposed to within individual farm or experimental populations. Modelling at this scale was made possible by the abundant data collected under an official surveillance programme. The modelling and associated analysis may provide an initial framework for analysis of other emerging diseases in aquaculture, such as bacterial kidney disease in farmed Scottish salmonids.

The model described is simple and there is considerable potential for expansion, for example modelling individual farms with different networks of interactions, rather than the simple random mixing of infection between all susceptible and infected populations used in this model. Such complex models might be useful in analysis of effectiveness of strategic area management of IPNV or other diseases. However, this model has proved effective at replicating the observations and its simplicity makes analysis relatively straightforward and robust.

7. ACKNOWLEDGMENTS

8. REFERENCES

Anderson R.M. and R.M. May (1979) Population biology of infectious diseases: Part I. *Nature* 280, 361-367

Ariel, E., and N.J. Olesen (2002) Finfish in aquaculture and their diseases- A retrospective view on the European community. *Bulletin of the European Association of Fish Pathologists*, 22, 72-84

FRS (2003) The report of the aquaculture health joint working group on infectious pancreatic necrosis in Scotland. Fisheries Research Services, Aberdeen pp. 90

Lotz, J.M. and M. Andres Soto (2002), Model of white spot syndrome virus (WSSV) epidemics in *Litopenaeus vannamei*. *Diseases of Aquatic Organisms,* 50, 199-209

Murray, A.G., M. O'Callaghan and B. Jones (2003a). A Model of Spatially-Evolving Herpesvirus Epidemics Causing Mass Mortality in Australian Pilchards (*Sardinops sagax*). *Diseases of Aquatic Organisms* 54, 1-14

Murray, A.G., C.D. Busby and D.W. Bruno (2003b) Infectious pancreatic necrosis virus in Scottish Atlantic salmon farms, 1996-2001. *Emerging Infectious Diseases*, 9, 455-460

Murray A.G., W.A. Lechen, R. Kilburn and R.S. Raynard (2004) A case-control study for the identification of risk factors behind clinical outbreaks of infectious pancreatic necrosis (IPN). Fisheries Research Services Marine Laboratory Report 06/04 pp 23

Murray AG and E.J. Peeler (2005) A framework for understanding the potential for emerging diseases in aquaculture. *Preventive Veterinary Medicine* 67, 135-147

Reno P.W. (1998) Factors involved in the dissemination of disease in fish populations. *Journal of Aquatic Animal Health* 10, 160-171

Smith G., J. Bebak and P.E. McAllister (2000) Experimental infectious pancreatic necrosis infections: propagative or point-source epidemic? *Preventive Veterinary Medicine* 47, 221-241

Stagg, R.M. and R.J. Smith (2003) Scottish fish farms annual production survey 2002. Fisheries Research Service, Aberdeen pp. 53

Swinton J., Harwood, J., Grenfell, B.T., Gilligan, C.A. (1998). Persistence thresholds for phocine distemper virus in harbour seals *Phoca vitulina* metapopulations. *Journal of Animal Ecology* 67, 54-68