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Evaluating effects of different control strategies for Infectious Salmon Anaemia (ISA) in marine salmonid farming by scenario simulation using a disease transmission model

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ABSTRACT

Infectious salmon anaemia (ISA) is an important viral disease causing economic losses and reduced welfare in farmed Atlantic salmon. Here, we present a spatio-temporal stochastic model for the spread of ISA between and within marine aquaculture farms. The model is estimated on historical production data for all marine salmonid farms in Norway from 2004 to February 2019. In this time 142 outbreaks of ISA occurred. We find that transmission from infected neighbouring farms accounts for around 50% of the infections, whereas transmission from "non-specified sources" accounts for around 40%. We hypothesise that the most important of the latter are viruses mutating from the non-virulent ISAV HPR0 to the virulent ISAV HPRdel. The model is used for scenario simulation, or what-if analysis, to investigate the effects of potential strategies to combat ISA, including screening, vaccination and culling. Changing from the current strategy of culling farms with detected ISA-outbreaks to mandatory screening and culling when virus is detected will reduce the fraction of cohorts with a clinical ISA outbreak from 3.8 to 0.36%. Introducing mandatory vaccination would have approximately the same effect as the current stamping-out strategy. The scenario simulation is a useful tool for deciding on appropriate mitigation measures.

1. Introduction

Infectious salmon anaemia (ISA) is an important disease causing economic losses and reduced welfare in farmed Atlantic salmon (*Salmo salar* L.). It is caused by Infectious salmon anaemia virus (ISAV) which belongs to the family *Orthomyxoviridae* (Kawaoka et al., 2005). There are two variants of ISAV, a non-virulent ISAV, termed ISAV HPR0, and a virulent variant, ISAV HPRdel. There are multiple ISAV HPRdel strains with varying origins (Fourrier et al., 2014). Infections with ISAV HPRdel induce ISA, a systemic and lethal condition characterised by severe anaemia, haemorrhaging and organ necrosis (OIE, 2019). ISAV HPR0 does not cause significant systemic infection and it has been found to be prevalent on gill and mucosal surfaces both in wild fish, in the freshwater smolt-producing phase and in the marine on-growing phase of salmon farming in the Faroe Islands and Norway (Christiansen et al., 2011; Lyngstad et al., 2012). ISAV HPR0 has been shown to be a progenitor of ISAV HPRdel, thereby representing a risk factor for the development of ISA (Christiansen et al., 2017). Outbreaks of ISA are mainly seen in the marine on-growing phase, with only a few cases being reported from the freshwater phase (OIE, 2019). Morbidity and mortality are variable, however the cumulative mortality may exceed 90% in outbreaks where no intervention is applied (OIE, 2019). All major salmon producing countries have reported ISA outbreaks (OIE, 2019), with the most recent large-scale epidemic occurring in Chile between 2007 and 2009 (Mardones et al., 2009) reducing production from 379 000 tonnes in 2007 to 98 000 tonnes in 2010 (Asche et al., 2010).

Norway experienced a large ISA epidemic from 1989 to 1992, which peaked in 1990 with outbreaks reported from 80 farms that year (Jansen et al., 2021). Between 1993 and 2019, the yearly number of farms experiencing ISA ranged from one to 20, with an annual average of 12 outbreaks over the past seven years (2013-2019) (Jansen et al., 2021). The number of outbreaks in 2020 is the highest since the early 1990s (23 cases) (Jansen et al., 2021).

ISA is notifiable in Norway, by the World Organization for Animal Health and within the European Union (EU) (Council Directive 2006/88/EC). As a result, there is a legal obligation to report suspicion of ISA,

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including the detection of ISAV HPRdel, in Norway to the Norwegian Food Safety Authority (NFSA). Following a suspicion, the NFSA performs fish sampling at the suspected farm, and submits the samples to the national ISA reference laboratory for diagnostic investigation. Confirmed ISA is reported to the NFSA who determines the official diagnosis for the farm and makes decisions on the implementation of control measurements. The latter includes establishment of a containment area and restrictions on fish movement. In addition, there is typically a requirement of depopulation of affected farms within a defined time period.

Control and mitigation of ISA are based on containment. Vaccines are available, but they do not offer complete protection against infection, and do not seem to hinder shedding from infected fish (Kibenge et al., 2004). Vaccination is not used in the official control program for ISA in Norway today, but has been used in North America, Chile and the Faroe Islands for some time (OIE, 2019).

We have previously developed a spatio-temporal stochastic model for the spread of infectious diseases between and within aquaculture farms, and applied it to model pancreas disease (PD), another important disease in the production of salmonids in the North Atlantic (Aldrin et al., 2015). This model has been used for simulating outbreak scenarios under different conditions (Bang Jensen et al., submitted). Here, we have adapted the model to simulate transmission of ISA. Since there are much fewer outbreaks of ISA compared to PD, and thus less data to estimate the model parameters, the ISA model is slightly simplified compared to the PD model.

Finally, the estimated model is used for scenario simulation, or what-if analysis, to investigate the effects of potential strategies to combat ISA, including screening, vaccination and culling.

2. Data

Our data covers the period from January 2004 to February 2019. In this period 1475 farms have been active, i.e. produced salmonids, and for each of these we have monthly data for the numbers of fish, the mean weights of fish and whether outbreaks of ISA were detected in given farms and months. 93% of the stocked fish are Atlantic salmon (*Salmo salar* L.), and the rest are rainbow trout,(*Oncorhynchus mykiss*). 98.5% of the fish are at farms containing either Atlantic salmon alone or both species together (but in different cages). For simplicity, we do not distinguish between these two species, even if it is known that rainbow trout is less affected by ISA than Atlantic salmon (Alarcón et al., 2020).

Furthermore, we know the geographic location of each farm and its seaway distances to all other farms (truncated from above at 100 km). In addition, we have data on the seawater temperatures, but these are not used in the model, instead we model seasonality explicitly.

The fish are usually stocked as smolts, at around 100-250g, and slaughtered around 1 1/2 year later at 4-5kg. After a production period, a farm is fallowed for some months before new fish are stocked. We use the term cohort for the fish population at a farm during a production period from stocking to slaughter. We assume that cohorts with start weight larger than 250g have not been stocked as smolt, but has been relocated, i.e. moved from another farm, and these constitute 27% of the cohorts in the data. The data consists of 6829 cohorts, with a total of 106 654 farm-months of production. 587 and 560 cohorts were active at the start and the end of the data period, respectively.

Fig. 1 shows the farms that were active at any time in the data period in an area on the West coast of Norway. In January 2018, 36 farms were actively producing salmonids. One of these had a clinical outbreak at that time, and three more farms got an outbreak later in the same production period.

The seaway distances between between pairs of active farms play a prominent role in our model. An active farm has on average 0.47 and 1.1 other active farms within a seaway distance of 3km and 5km, respectively (Fig. 2). Seaway distances are easy to compute for all farms, but they ignore local sea current conditions. The importance of hydrodynamics has been demonstrated by Gustafson et al. (2007) for ISA and by Viljugrein et al. (2009) and Stene et al. (2014) for PD. Therefore,

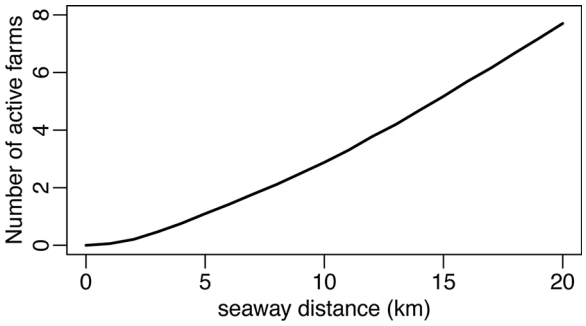

Fig. 2. The number of other active farms within a given seaway distance from an active farm, averaged over the data period and over all farms.

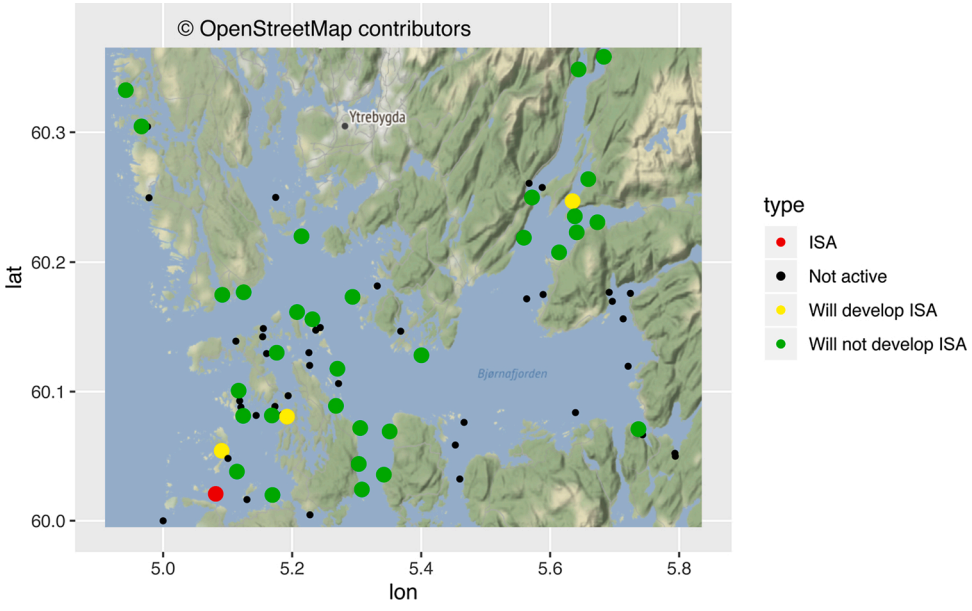

Fig. 1. Location and production status of salmonid farms in an area of West Norway in January 2018. Black dots indicate farms that were active in at least one other month in the data period, but not in January 2018. The 36 other farms did produce salmonid during this month, and the colour codes indicates whether they i) at that time had a clinical ISA outbreak (red dots), ii) got an outbreak later in the same production period (yellow dots), or iii) removed the fish later without an outbreak (green dots).

distance measures based on hydrodynamic models could be an interesting alternative to seaway distances, but we do not have such information for the whole Norwegian coast.

The monthly number of active farms varies systematically during a year, but have been quite stable over time (Figure 3, panel a), whereas the number of fish per farm has increased (352 000 in average in 2004 vs. 728 000 in 2018, Figure 3, panel b). 83% of the cohorts were stocked during April-October (89% in 2004 and 78% in 2018, Figure 3, panel c). The monthly number of clinical ISA outbreaks was on average 0.78 (142 outbreaks in total) and varied between 0 and 7 (Fig. 3, panel d).

3. Model framework

The full model is divided into three sub models: i) Initial infection of a farm, which include infection from infected neighbouring farms, ii) internal development of disease within the farm, modelled by a susceptible-infected-recovered (SIR) model, and iii) development of a clinical outbreak in the farm. The model parameters are estimated on disease and production data from January 2004 until February 2019. The disease data consist of dates for clinical outbreaks, which are mandatory to report, but the times of infections are unknown.

It is possible for fish to be infected in the freshwater phase, and we thus assume that a fish cohort has a probability ρ_0 for already being infected when the cohort was stocked as smolts. Fish can also have been infected in another farm and relocated. In this case, we assume a probability ρ_r. Most fish cohorts are uninfected at stocking and thus considered susceptible. These can be infected with a rate $\lambda(t)$ which varies over time, depending on the infection status at the neighbouring farms and the seaway distances to them, in addition to a time-independent background transmission rate. Once a cohort is infected, the fraction of infected fish, $I(t)$, evolves over time according to an SIR model, depending on the time of year. Furthermore, an infected fish cohort may develop a clinical outbreak with a time varying rate $\kappa(t)$ which is proportional to $I(t)$. Finally, the fish cohort is removed (either slaughtered or moved to another farm), and at time of removal it may either be uninfected, infected without a detectable clinical outbreak or infected with a clinical outbreak. The model is estimated by a Bayesian approach using latent variables to represent the unobserved infection process and other unobserved quantities. In the following, we describe the various sub-models. Further details on the various elements of the model and the estimation procedure are given in Aldrin et al. (2015) (Fig. 4).

3.1. The infection process model

Let $\lambda_i(t)$ denote the infection rate for a given susceptible fish cohort i at a given time t. $\lambda_i(t)\mathrm{d}t$ is then approximately the probability that the cohort will be infected in the small time interval from t to $t+\mathrm{d}t$. The infection rate has unit 1/month, whereas all other quantities are unitless. The infection rate has the following additive-multiplicative structure

$$\lambda_i(t) = \delta_i^{\text{susc}}(t)\cdot\omega_i(t)\cdot[\lambda_i^d(t) + \lambda_i^p(t) + \lambda_i^o(t)]. \quad (1)$$

When multiplied by the two terms outside the squared brackets, the three additive terms in Eq. (1) represent alternative transmission pathways:

- $\lambda_i^d(t)$, the rate of infection from infectious fish cohorts in the neighbourhood, due to waterborne transmission of the ISA virus, depending on the seaway *distance* to infected fish cohorts. It is decomposed into the sum of contributions from each neighbouring cohort j, denoted $\lambda_{ij}^d(t)$, such that $\lambda_i^d(t) = \sum_{j\neq i}\lambda_{ij}^d(t)$. The contribution from cohort j is modelled as

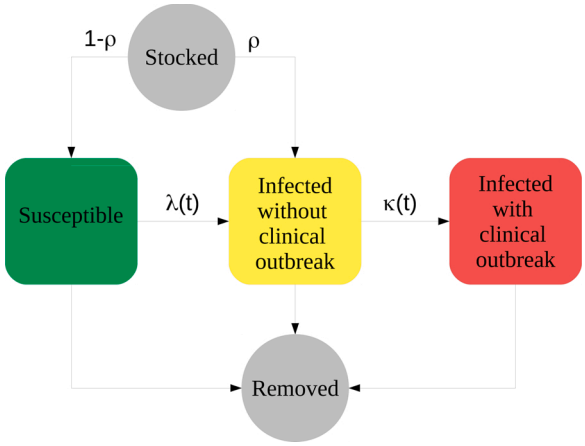

Fig. 4. Overview of the model. The ρ parameter is equal to ρ_r for relocated fish cohorts and ρ_0 otherwise.

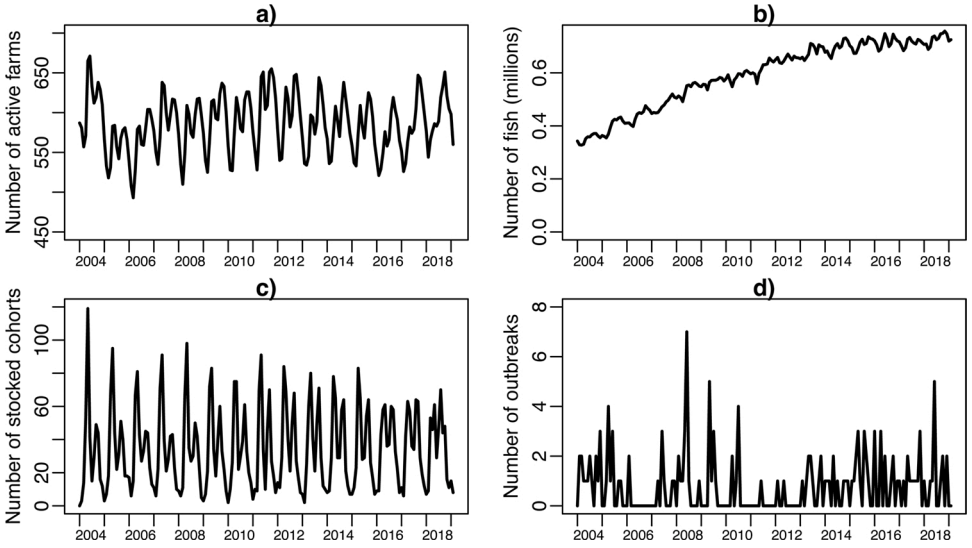

Fig. 3. Time plots of monthly values of a) the number of active farms, b) the average number of fish per farm (in millions) c) the number of stocked cohorts per month, including relocated cohorts, d) the number of clinical ISA outbreaks.

$$\lambda_{ij}^{d}(t) = \phi \cdot exp(-\phi \cdot (d_{ij})^{\alpha} \Big/ \alpha) \cdot I_j(t), \quad (2)$$

where: i) d_{ij} is the seaway distance (Section 2 and Fig. 2) between fish cohorts i and j measured in kilometres; ii) ϕ and α are parameters that express the effect of the seaway distance for the risk of infection; and iii) $I_j(t)$ is the fraction of fish infected at a neighbourhood cohort j at time t. Both ϕ and α are included twice in Eq. (2), to make these parameters less correlated with each other and with other parameters. However, by a simple re-parametrisation of the full model, this part of the model could equivalently be written in the simpler form $exp(-\phi^{*} \cdot (d_{ij})^{\alpha}) \cdot I_j(t)$, where $\phi^{*} = \phi/\alpha$.

- $\lambda_i^p(t)$, the rate of infection attributed to *previous* infected fish cohorts at the same fish farm as cohort i, due to remaining ISA virus at or near the farm. This is modelled as

$$\lambda_i^p(t) = \zeta \cdot \delta_i^{\text{prev}}, \quad (3)$$

where δ_i^{prev} is a latent indicator variable being 1 if a previous fish cohort at the same farm was infectious at most six months prior to stocking of the current fish cohort i and 0 otherwise. The parameter ζ expresses the effect of previous infected cohorts.

- $\lambda_i^o(t)$, the rate of infection via *other*, non-specified, pathways. In the case of ISA, this is most likely due to the non-virulent HPR0 virus developing into the virulent HPRdel, even though other factors, such as vessels visiting farms (Murray et al., 2002; Mardones et al., 2014), may be present. This is simply modelled as

$$\lambda_i^o(t) = \theta_0, \quad (4)$$

where θ_0 is a non-negative parameter.

The two multiplicative factors in Eq. (1) are:

- $\delta_i^{\text{susc}}(t)$, a latent at-risk indicator being 1 when fish cohort i is susceptible and 0 otherwise.
- $\omega_i(t)$, a time-varying proportionality factor common for all three transmission pathways. In the current version, it accounts for a possible trend common for all farms, and the number of fish at farm i, and is modelled as

$$\omega_i(t) = exp(\psi_0 + \psi_1 \cdot l(t) + \beta^n \cdot x_i^n(t)). \quad (5)$$

Here, $l(t)$ is a linear function increasing from -1 at the start of the data period to 1 at the end of data period. Furthermore, $x_i^n(t) = log(n_i(t)) - \overline{log(n)}$, where $n_i(t)$ is the number of fish in cohort i in month t, and $\overline{log(n)}$ is the mean of $log(n_i(t))$ taken over all cohorts and months. The ψ_k-s and β^n are parameters.

3.2. An SIR model for internal disease dynamics

We assume that the cohort-internal epidemic follows an SIR model (Anderson and May, 1991). We let $S_j(t)$, $I_j(t)$ and $R_j(t)$ denote the fractions of susceptible, infected and recovered fish in cohort j at time t, where $I_j(t)$ is included in Eqs. (2). Then $S_j(t) + I_j(t) + R_j(t) = 1$. At the time cohort j becomes infected, $I_j(t) = I_0$ and $S_j(t) = 1 - I_0$, where I_0 is a constant parameter. An SIR model is usually defined by a set of differential equations in continuous time, but this is computationally demanding since it involves integration. Instead, we first evaluate the process states at discrete, monthly time steps by

$$S_j(t+1) = -\eta_j(t') \cdot I_j(t) \cdot S_j(t), \quad (6)$$

$$I_j(t+1) = \eta_j(t') \cdot I_j(t) \cdot S_j(t) - \nu \cdot I_j(t), \quad (7)$$

where the time unit is month. The fractions of infected fish at intermediate times $t < t' < t+1$ are further linearly interpolated by $I_j(t') = [1 - (t' - t)]I_j(t) + (t' - t)I_j(t+1)$. We assume that the recovery rate ν is constant, but let the transmission rate η vary smooth by the time of the year as

$$\text{logit}(\eta_j(t')/10) = \eta_0^S + \eta_{s1}^S sin(2\pi Y(t')) + \eta_{c1}^S cos(2\pi Y(t')), \quad (8)$$

and in addition we truncate the product $\eta_j(t')I_j(t)$ to be at most 1, if necessary. Here, $Y(t')$ denotes the time of the year for time t', being 0 at the start of a year and 1 at the end of a year.

3.3. The outbreak process model

Let $\kappa_i(t)$ denote the outbreak rate for a fish cohort i at time t, with unit 1/month. We assume that this outbreak rate is proportional to the fraction of infected fish $I_i(t)$, and given by

$$\kappa_i(t) = exp(\kappa_0) \cdot I_i(t), \quad (9)$$

where κ_0 is a parameter common for all cohorts.

Table 1
Overview of parameters with posterior means and 95% credible intervals for the ISA model. The last two parameters are used in initialisation at the start of the data series, but not described in the text here. See Aldrin et al. (2015) for the definition of these.

Parameter description	Parameter symbol	Posterior mean	95% C.I. lower	95% C.I. upper
P(infected at stocking)	ρ_o	$0.86 \cdot 10^{-3}$	$0.02 \cdot 10^{-3}$	$2.56 \cdot 10^{-3}$
P(infected at stocking relocated)	ρ_r	$9.70 \cdot 10^{-3}$	$4.05 \cdot 10^{-3}$	$17.68 \cdot 10^{-3}$
Distance effect	ϕ	0.48	0.25	0.70
Distance transformation	α	0.50	0.33	0.74
Effect of previously infected cohorts	ζ	$2.31 \cdot 10^{-3}$	$0.04 \cdot 10^{-3}$	$10.69 \cdot 10^{-3}$
Effect of other sources	θ_0	$0.55 \cdot 10^{-3}$	$0.16 \cdot 10^{-3}$	$1.32 \cdot 10^{-3}$
Susceptibility factor, intercept	ψ_0	0.25	−0.65	1.27
Susceptibility factor, time	ψ_1	0.53	0.18	0.90
Susceptibility factor, log number of fish	β^n	0.30	0.02	0.59
Initial fraction of infected fish in SIR	I_0	0.12	0.04	0.23
Recovery rate in SIR	ν	0.10	0.01	0.27
Logit transmission rate in SIR, intercept	η_0	−2.91	−3.68	−1.75
Logit transmission rate in SIR, seasonal coef.	η_{s1}	1.04	0.35	1.84
Logit transmission rate in SIR, seasonal coef.	η_{c1}	−0.95	−1.81	−0.18
Log outbreak rate intercept	κ_0	−0.55	−1.31	0.31
Used in initialisation	θ_1	$1.15 \cdot 10^{-3}$	$0.18 \cdot 10^{-3}$	$3.38 \cdot 10^{-3}$
Used in initialisation	ξ	0.47	0.03	0.97

4. The estimated model

Table 1 show the posterior means and 95% credible intervals for the parameters in the model. The probability (ρ_o) for smolts being infected at stocking is around 0.1%, whereas the probability (ρ_r) for a relocated cohort being infected when it is re-stocked is around 1%. The susceptibility of a farm seems to increase during the study period (ψ_1 is positive), potentially due to increased average stocking numbers or increase in unmeasured stress events such as increased handling due to treatments against sea lice. Furthermore, the susceptibility is higher for a farm with many fish than for a farm with fewer fish (β^n is positive), which is reasonable. We also fitted models including the fish weight in the proportionality factor $\omega_i(t)$, and both the number and weight of fish at neighbouring farms in the term $\lambda_i^d(t)$ representing transmission from infected neighbouring cohorts. These were not significant, in contrast to the model for PD given in Aldrin et al. (2015), which may be because there are too few outbreaks of ISA to estimate such potential effects.

Panel a) in Fig. 5 shows how the risk of being infected from infected neighbouring farms decreases by increased seaway distance (described by the parameters ϕ and α). Compared to the risk at a distance of 0km, the relative risk of being infected is reduced to 20% at 3km, 13% at 5km, 6% at 10km, 3% at 15km and 2% at 20km. This is consistent with previous findings of rapid reduction in ISA risk with increasing distance between farms (Jarp and Karlsen., 1997) and the effectiveness of area management measures to control ISA as exemplified from Scotland (Murray and Gubbins., 2016). Panel b) shows how the transmission rate ($\eta_j(t^{'})$) in the SIR model varies seasonally over a year. Finally, panels c) and d) illustrates how the fraction of infected fish ($I_j(t)$) varies over time after the infection episode, depending on what time of year the cohort was initially infected. The maximum fraction of infected fish in a cohort infected in January reaches about 77% five months after infection, whereas the corresponding fraction is lower and reaches 64% if the cohort is infected in April. However, the maximum number of infected fish is reached after about half the time (3 months) in the latter situation.

The average time from infection to detection of an outbreak is estimated to be 4.6 months (C.I. 3.6-5.6 months) for those cohorts that experienced a clinical outbreak of ISA. We estimate that 3.2% of all cohorts were infected (C.I. 2.8-3.7%), and that 34% (C.I. 25-45%) of these were removed without any clinical outbreak. However, these include cohorts that were not slaughtered, but moved to another farm, so some of these may have experienced a clinical outbreak later.

The estimated relative importance for each of the various sources of infection is given in Table 2, computed as described in Aldrin et al. (2015).

Table 2
Relative importance (in %) of various sources of infection.

Source of infection	Posterior mean	95% C.I. lower	95% C.I. upper
Infected smolts at stocking	1.4	0.0	4.5
Infected, relocated cohorts	7.8	4.2	12
Infected by infected neighbours	50	42	58
Infection associated with previously infected cohorts	0.9	0	3.0
Infected from "non-specified sources" (HPR0)	39	30	49

Transmission from infected neighbouring farms accounts for around 50% of the infections. The proportion of ISA cases officially classified as having another infected farm as the likely source of infection varies between years. This is natural given that for example farm density in affected areas will impact the likelihood of between-farm spread of ISAV. Classification will also be influenced by the level of imperfect information present. If an unidentified ISA infection occurs in one farm this may result in an ISA case being assigned as an unknown source of infection when it should truly be classified as spread from neighbouring farm had the infection been known. Infection from "non-specified sources" accounts for around 40% of the infections, and for ISA we believe that the most important of these are viruses mutating from the non-virulent ISAV HPR0 to the virulent ISAV HPRdel. This is in line with a previous publication where the annual risk for a farm having an ISA outbreak with an unknown source was 0,7% (Lyngstad et al., 2018). In our case, with an average of 589 active cohorts and an average of 9.4 ISA cases per year, of which 39% is assumed to originate from "non-specified sources", this would equate to 0,6% of active farms. Infected cohorts moved from another farm accounts for 8%, and most of these are presumably originally either infected by surrounding farms or by "non-specified sources" before they were relocated. This is in line with observed practise, where fish from farms known to be infected but without clinical disease are sometimes split to neighbouring farms due to stocking density levels. Infection from the freshwater phase, through the stocking of infected smolts, is rare and accounts for around 1% of all infections. Infections associated with previously infected cohorts at the same farm seem to be negligible for ISA, which is consistent with the

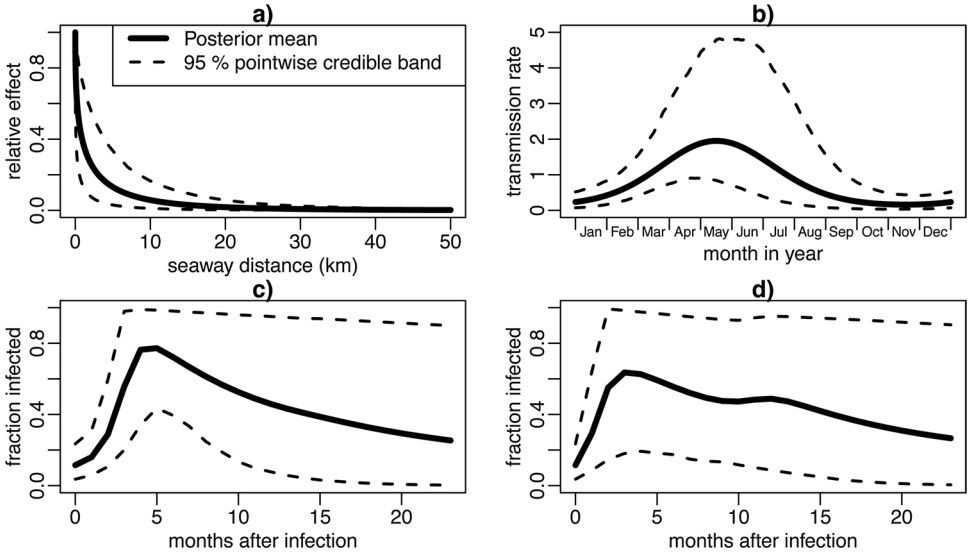

Fig. 5. Selected results from the estimated model. a) Relative effect of the seaway distance. b) Transmission rate as a function of time of year. c) Time development of the fraction of infected fish in a cohort infected 1 January. d) Time development of the fraction of infected fish in a cohort infected 1 April.

relatively short ISAV survival times reported for seawater (Tapia et al., 2013; Rimstad et al., 2011). It is also a consequence of the official restrictions on putting fish to sea following an ISA outbreak. A farm that has experienced ISA may not be restocked until after a two-month coordinated fallowing period for all farms within the combat zone of the containment area, with the ISA infected farm itself being fallowed for a minimum of three months.

5. Evaluation of mitigation strategies by scenario simulations

When a farm is diagnosed with a clinical ISA outbreak, the company is usually required to slaughter all fish at the farm within few weeks. Based on a request from the Norwegian Food Safety Authority to investigate other strategies as alternatives to today's practice, we have performed scenario simulations of different strategies for control. These include:

- 1a) No restrictions, the fish are slaughtered at "normal time", i.e. as the same time as non-infected cohorts (a so-called "laissez-faire" strategy)
- 1b) As 1a, but with mandatory vaccination of all cohorts against ISAV. Currently there is one multivalent vaccine against ISA available in the Norwegian market, however field-data on the true population-level protection against infection is currently unavailable. We let the vaccine reduce the probability of infection by 50% during the whole production time in sea.
- 2a) Mandatory slaughtering 6 weeks after a clinical outbreak. This is relatively similar to today's practice, and serves as a baseline scenario.
- 2b) As 2a, but including mandatory vaccination as described in 1b.
- 3a) Mandatory screening of 20 fish from all farms each fourth week, and mandatory slaughtering 6 weeks after a positive ISAV test-result in at least one fish.
- 3b) As 3a, but in addition mandatory vaccination.

These scenarios are related to a new regulation on animal health that will come into force within EU from April 2021 (Regulation (EU) 2016/429). Within this regulation, ISA will be classified as a category C disease, allowing optional eradication programmes to be put in place in EU- and European Economic Area countries. Several different control strategies may be envisioned as appropriate for the control of ISA in Norway and other salmon-producing countries, including use of screening programs, mandatory vaccination or stamping-out. All scenarios are founded on the basic biosecurity measure of local coordinated fallowing, thereby minimising the potential for between-generation spread of infections within sites.

We investigate this by using the described ISA model for scenario simulations or what-if analysis. We base the simulations on 10 years of historical production data from March 2009 to February 2019 to make the simulations as realistic as possible with respect to production aspects that are not handled by the model, including the locations of farms, the times of stocking and slaughtering, the number of active farms and the number of fish per farm. The number of farms have been quite stable in this period, but the number of fish per farm have increased (Figure 3, panels a) and b)). As we wanted to simulate scenarios for the future, we adjust the historical number of fish per farm so it is roughly on today's level in the following way:

- Let $f_0 = 0.421$ and $f_1 = 0.541$ denote the average monthly number of fish (in millions) per active farm between March 2007 and February 2009 and between March 2017 and February 2019, respectively.
- Fit a curve $f(t) = f_0 + b_1(t - t_0) + b_2(t - t_0)(t - t_1)$ for the monthly number of fish per farm on data from March 2009 to February 2019. Here, t_0 is the March 2009, t_1 is February 2019, and t is any month on this period. The parameters b_1 and b_2 are estimated to be 0.00099 and -0.00001, respectively. The time unit is month.
- For a cohort stocked before March 2009, the monthly number of fish for this cohort as multiplied by the factor f_1/f_0.
- For a cohort stocked later, the monthly number of fish is multiplied by the factor $f_1/f(t)$.

This adjusted historical production series will then act as a hypothetical future production series ten years ahead starting at March 2019.

The estimated model parameters, including the infection statuses of each farm in February 2019, are uncertain and described by the joint posterior distribution of the parameters. The posterior distribution is represented by a set of samples of parameter values, given as output from the estimation procedure, which is based on Markov Chain Monte Carlo (MCMC) estimation. To take this estimation uncertainty into account in the scenario simulations, each simulation starts by drawing a random parameter set, common for all scenarios.

As mentioned above, scenario 2a is relatively similar to today's practice. Therefore, this scenario should give roughly the same number of outbreaks as in the historical data since 2015. To achieve this, we eliminated the effect of the time trend by setting the parameter ψ_1 (of Eq. (5) and Table 1) to 0.

Conditioned on the sampled parameter set, we then initiate the infection status of each farm at the beginning of March 2019 in this way:

- 234 farms are active both in the real February 2019 and the hypothetical March 2019. These are assigned the infection status ($S_i(t)$, $I_i(t)$ and $R_i(t)$) they had in February 2019, and whether they have had a clinical outbreak or not.
- 326 farms are active in February 2019, but not in the hypothetical March 2019. These are not used below.
- 270 farms are active in the hypothetical March 2019, but not in February 2019. The infection status for these 270 farms are found by randomly drawing infection statuses ($S_i(t)$, $I_i(t)$ and $R_i(t)$) from the 326 possibilities, without replacement, but under the constraint that the fraction of infected farms are the same as in February 2019.

For each scenario, we simulate from the model how ISA evolves over time 10 years ahead, conditioned on the parameter set, including the initial infection statuses, and the hypothetical production history. If a cohort is slaughtered due to ISA, the production length for this specific cohort is shortened, but the next cohort is put to sea at the same time as in the original data. Screening is implemented as 20 fish being randomly drawn each fourth week from each farm, with a probability $I_i(t)$ for each of these to be infected and detected by a test with 100% sensitivity. The effect of vaccination is implemented by reducing the proportionality factor $\omega_i(t)$ by 50%. 200 simulations are performed for each scenario.

Fig. 6 shows the monthly number of clinical outbreaks for each strategy, averaged over the simulations, together with observed numbers from 2015 until February 2019. The simulations the first 22 months can also be compared with updated data. In 2019, there was in total 10 ISA outbreaks, and 23 in 2020. Strategy 2a keeps the number of

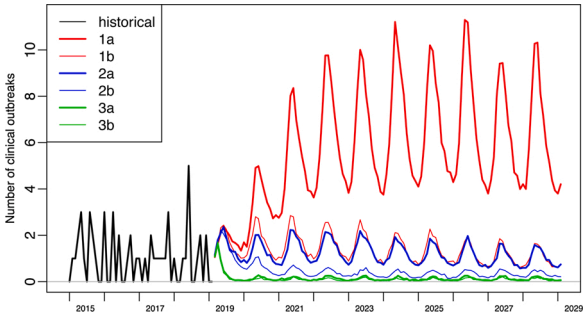

Fig. 6. Monthly averages of the number of outbreaks in scenario simulations representing six different scenarios from March 2019, together with observed data until February 2019. For explanation of the scenarios, refer to the text.

ISA outbreaks on roughly the same level as the past few years (14.7 per year compared to 12.8 per year on average in the period 2015-2018). This similarity between the model results and the observed level of outbreaks suggest that the model is sufficiently able to represent the true situation, making the scenario simulation results appropriate as a decision-making support tool in the Norwegian setting.

Abandoning the mandatory culling without any other preventive measure (strategy 1a) will increase the number of outbreaks dramatically, and such a high number of ISA cases would likely be considered as non-viable by all stakeholders. However, the model does not consider the possibility of industry actors joining forces and initiate voluntary control measures to avoid an escalation of the magnitude shown by strategy 1a. This could for example be at regional level, even if it might not be feasible to include the entire country. The model considers measures at farm-level, while voluntary measures could be expected to be initiated at least partly at cage-level within affected farms. It is possible that cage-level measures may be instigated faster than farm-level measures both for logistical and economic reasons. The likelihood and feasibility of optimal voluntary measures throughout the industry as a whole, and the effect of cage-level measures relative to the modelled results, remain unknown. However, it seems that introducing mandatory vaccination (strategy 1b) is equally effective as today's culling strategy alone (strategy 2a), if the vaccine used has the modelled efficacy. In essence these results highlights the importance of infection control in relation to reducing the number of ISA cases. Any biosecurity measures, alone or in combination, that are able to reduce the likelihood of infection similarly will have a significant effect. Introducing mandatory screening combined with culling will bring the number of outbreaks to a low number, because infected cohorts usually are slaughtered before an outbreak occurs. Qviller et al. (2020) have previously shown that the number of new farms being infected increases with increased time lapse between the ISA diagnosis and the start of the depopulation at an infected farm. However, the present legal requirement of a clinical ISA diagnosis before mandatory depopulation means that such a measure would currently be based on voluntary action from the producer.

From a common starting point in March 2019, the monthly averaged number of outbreaks diverge for the various strategies, and are roughly stabilised on a new level after two years. Therefore, we have averaged the results over the last eight years of the simulation period. In this period, there were in average 554 active farms each month, with in total 300 millions fish, and 418 production cycles were completed per year. Table 3 shows various fractions. The relative effect of vaccination is larger when this is the only preventive measure, since vaccination reduces the number of outbreaks with 80% in changing from strategy 1a to 1b (18.4% vs. 3.8% of the cohorts experience an outbreak), but only with 1/3 when changing from strategy 3a to 3b. Strategies 3a and 3b, screening followed by mandatory slaughter after a positive test, minimise both the number of outbreaks and the number of undetected infections, since the whole fish cohort is slaughtered soon after a positive test. However, we remind the reader that a vaccine giving 50% population-protection against infection has not yet been documented.

Table 3
Fractions (in %) of cohorts with clinical outbreaks, undetected infection and mandatory slaughter, and fraction of total production time after a clinical outbreak.

Scenario	Fraction of cohorts with clinical outbreaks	Fraction of cohorts with undetected infection	Fraction of cohorts with mandatory accelerated slaughter	Fraction of total production time after a clinical outbreak
1a	18.4	5.7	0.0	8.9
1b	3.8	1.4	0.0	1.9
2a	3.4	1.4	3.4	0.28
2b	1.0	0.38	1.0	0.08
3a	0.36	0.05	1.7	0.02
3b	0.24	0.02	1.0	0.01

6. Discussion

The selection of a control-strategy for any infectious disease involves taking into consideration a range of factors, including balancing animal health, economic and political consequences. Thus a seemingly ideal strategy from one viewpoint may be considered to have unacceptable side effects that prevents its implementation. Scenario modelling, in combination with cost-benefit analyses, have previously been used to highlight epidemiological and economic effects of various control strategies against pancreas disease in Norwegian salmon farming (Pettersen et al., 2016). Unfortunately cost-benefit analyses for the modelled strategies against ISA could not be conducted, primarily due to the lack of cost data in combination with limitations on available time and resources. As ISAV is listed by the OIE there is a continuous risk of trade restrictions, which potentially could become more frequent as the number of countries that initiate salmon farming increase. Due to the current depopulation strategy there are limited data available on the likely mortality-levels during ISA outbreaks in today's farms using modern technology. This hinders calculations of the economic consequences of outbreaks, and subsequently of the cost-benefits of control programs. Additionally, there are important factors that are almost impossible to quantify and/or monetise, such as improved fish welfare. Infection with ISAV might also render the fish more susceptible to other diseases. From a fish welfare perspective, a strategy that minimise the infection risks, irrespective of whether or not the infection results in a clinical outbreak, is optimal. A high disease burden and/or perceived poor fish welfare may give the aquaculture industry a poor reputation amongst national and international consumers, which may influence salmon prices and market shares. With a disease like ISA where there are a limited number of outbreaks per year the control costs is carried by the (relatively) few affected farms in order to protect the remainder of the industry. There are currently no compensation systems or similar in place for affected companies. In hard hit areas there may also be major consequences in associated industries following prematurely removed fish populations in the form of cancelled contracts and reduced delivery of raw materials.

The main direct economic cost of strategy 1a is due to increased fish mortality following a clinical outbreak. In addition, there are likely external effects for neighbouring producers as a result of infection spreading from infected farms. For strategy 1b, and the other strategies involving mandatory vaccination, there will be an added cost of an ISAV vaccine (if monovalent) or an additional ISAV-component (if multivalent). Even at a relatively low cost per dose the overall cost to the industry will be significant given the vast number of smolts put to sea each year. (The median number of smolt put to sea at a Norwegian sea farm in 2018 and 2019 was 823 383.) Avoided costs as a result of prevented ISA infections from vaccination are highly uncertain due to the lack of field effect data. While vaccination may be cost-effective in areas experiencing larger ISA outbreaks, a high proportion of vaccinated fish are likely to never be exposed to the virulent variant of the ISAV. However, if a vaccine should be deemed sufficiently effective to avoid depopulation at cage level in a vaccinated population that test ISAV positive, the benefit of vaccinating may be significantly increased.

In scenarios 2a and 2b, significant direct costs will be incurred in farms where depopulation is required while some of the fish (3.4% for 2a and 1.0% for 2b) are slaughtered before the optimal slaughter weight has been reached. This is also an important cost for strategies 3a and 3b (1.7% and 1.0% are slaughtered prematurely), with the addition of screening costs. Any strategy involving mandatory inspections by government staff will incur additional inspection costs that may be shouldered by the public, the producers or via a public-private cost sharing.

This study shows how disease scenario modelling may be used to support decision making. While there may be uncertainties associated with the various parameters and the exact number of outbreaks and infection events that can be expected with each strategy, the relative differences between the outcomes of the different scenarios should

provide a valuable input to the knowledge-pool on which strategy selections should be based.

Conflict of interest

None declared.

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