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Evaluating abnormal mortality as an indicator of disease presence in the Atlantic salmon industry using the receiver operating characteristic (ROC)

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ABSTRACT

Aquaculture faces many threats, including diseases, of which some are notifiable under current UK regulation, e.g. infectious salmon anaemia (ISA) and infectious haematopoietic necrosis (IHN). Abnormal mortality is one possible indicator of the presence of infectious disease on a site that may be used, by the regulator, as a surveillance alert that allows them to identify possible notifiable diseases and to activate measures of control to reduce the risk of spreading those diseases. Therefore, mortality records at the farm level may be a useful indicator for regulatory surveillance purposes in order to identify potential disease outbreaks. In the UK, regulators and producers have discussed abnormal rates of mortality that may be considered as a trigger to notify the official regulator. In our study, the receiver operating characteristic (ROC) approach was used on mortality data from production cycles of a site production database of marine Atlantic salmon belonging to a single company. The usefulness of these data in helping the detection of infectious diseases was determined using measures of sensitivity and specificity. For fish under 750 g, the abnormal rates of mortality did not provide a strong indication of the presence of disease. The area under the curve ($0 \leq AUC \leq 1$) values were generally low with the exception of cardiomyopathy syndrome (CMS) that showed $AUC = 0.77$ for weekly mortality and $AUC = 0.73$ for five-week rolling mortality. However, abnormal levels of mortality for fish with weight over 750 g provided a strong indication of the presence of disease with the exception of both *suspected* and *confirmed* IPN. The probabilities of triggering official notification were low since mortality events over the percentages proposed happened infrequently. The most efficient trigger will be for weekly mortality (1%) for fish with weight over 750 g since abnormal mortalities in such large fish are more likely to be associated with the presence of disease.

1. Introduction

The control of diseases is essential to the profitable production of any farmed species (Menzies et al., 1996). In the UK, legislation was first implemented to prevent the introduction and spread of serious fish diseases under the Diseases of Fish Act 1937, which introduced the legal requirement to notify the competent authority of suspicion or presence of certain diseases in fish (McVicar, 2002). Additionally, the finfish aquaculture sector in Scotland is supported by a code of good practice (Anonymous, 2010) that provides guidelines to reduce the risk of spreading disease. The guidelines from the code of good practice aim to prevent the spread of infection by providing standards for management of fish disease. These standards incorporate a set of measures to be implemented regardless of disease history (e.g. basic biosecurity measures and fallowing) and a set of measures to be implemented when suspicion and/or confirmation of diseases occurs, consisting of disease control measures such as movement controls or culling. The code of good practice in conjunction with the legislation of Diseases of Fish (control) Regulations (SI 1994 No 1447), introduced in 1994, implemented measures of disease control that are required when suspicion or confirmation of a disease outbreak occurs. The Fish Health Regulations 1997 (SI 1997 No 1881) were introduced in 1997 to control the movement of live molluscs and live fish, their eggs and gametes as well as certain dead fish into the UK from elsewhere in the EU. The Aquaculture and Fisheries (Scotland) Act 2007 was introduced in 2007 to regulate against the unauthorised introduction of fish to inland waters and for the control of *Gyrodactylus salaris*.

As part of these legislations, the regulator requires notification to the official services of the suspicion of certain diseases – notifiable diseases – such as infectious salmon anaemia (ISA) and infectious haematopoietic necrosis (IHN), in order to carry out surveillance. However, surveillance resources are necessarily limited, so their most efficient use is through risk-based surveillance whereby sampling is concentrated on sites that are most likely to be infected

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(Stark et al., 2006). The recent Chilean outbreak of ISA (Henson, 2008; Mardones et al., 2009; Vass, 2010) illustrates the threats and the impacts of disease in the aquaculture industry and the importance of a good regulation and husbandry practices to reduce the impact of spread of infectious disease. In Scotland, the early implementation of regulations largely contributed to the control of an ISA outbreak in 1998 (McVicar, 2002) and again in 2008–2009 in Shetland (Murray et al., 2010). In 2008–2009 during the ISA outbreak, Marine Scotland used farm-level mortality as an indicator of disease. Abnormal mortality rates alerted the Marine Scotland Science Fish Health inspectors to the area affected by ISA in 2008, and sampling based on this mortality allowed rapid detection that confined the disease to a small area of south-east Shetland (Murray et al., 2010).

The presence of abnormal mortality rates on a site is one possible indicator of disease. Different diseases may lead to different levels of mortality. Mass mortality can also be related with non-pathogen driven causes including natural causes such as storms or algal blooms (Pillay and Kutty, 2005; Soares et al., 2011). Nevertheless, farm-level mortality records are a potential indicator that may be used to trigger surveillance and allow the official authority responsible for fish health in Scotland, Marine Scotland, to control and study the frequency, the spread and the disease patterns within farmed fish populations.

The timely reporting of mortality above a threshold level may help target risk-based surveillance to achieve efficient use of surveillance resource. Potential mortality threshold values have been discussed with the industry and potential cut-off values selected by the regulator Marine Scotland in consultation with the industry (Richards, 2010). These thresholds are considered to be of value to identify when abnormal mortalities have occurred which could then be used for inspection alerts. The introduction of mortality thresholds may allow a rapid detection of the presence of notifiable diseases and activation of measures of appropriate disease control, where required. The optimal abnormal mortality threshold used to trigger surveillance is a trade-off between fewer missed true positive tests at the expense of more false alerts. An increased number of false alerts is an important factor in overall surveillance system cost.

The aim of this study was to explore how effective reported mortality would be at detecting the presence of outbreaks of infectious disease based on different mortality cut-off values and then to extrapolate further to allow for rapid detection of notifiable diseases. Since limited mortality information is available for notifiable diseases, production cycles from a site production database without notifiable diseases were used to analyse mortality patterns for infectious diseases and to support the identification of adequate mortality surveillance thresholds. Abnormal mortality percentages of 1.5% for weekly mortality and 6% for five-week rolling mortality for fish with average weights under 750 g and 1% for weekly mortality and 4% for five-week rolling mortality for fish with average weights over 750 g were tested in this analysis as potential thresholds, i. e., whether these thresholds were appropriate and useful for official regulators to be notified. In this study, the usefulness of mortality recorded at the farm level for aiding the detection of an infectious disease was assessed using measures of sensitivity and specificity, i.e., the probability that exceeding the cut-off rate of mortality is associated with the presence of disease (sensitivity) and mortality below the cut-off is associated with absence of disease (specificity).

1.1. Receiver operating characteristic (ROC)

In our study, the receiver operating characteristic method (ROC) was applied on mortality data from Atlantic salmon in seawater from a single company, which represented one third of total Scottish farmed salmon production in 2005 (Anonymous, 2005). This methodology was already used by Jansen et al. (2007) to assess the accuracy of a model prediction in aquatic animal health. For that, we used measures of sensitivity and specificity for each test across a variety of possible test thresholds. For such a test:

$$Sensitivity = True\ positive/(True\ positive + False\ negative)$$
$$Specificity = True\ negative/(True\ negative + False\ positive)$$

In many cases, the result of a diagnostic test is derived from a continuous measurement or test score, such as binding or reaction rate, and when the score exceeds a fixed reference value, called the threshold or cut-off value, the test is said to be positive (Schulzer, 1994). Once each test score is classified either positive or negative based on the cut-off value, the true positive and negative can be identified. A "condition" positive is considered "true" positive based on the cut-off value positive with a true disease status and a "condition" negative is considered "true" negative based on the cut-off value negative with a non-disease status. Sensitivity is then derived as the percentage of all true positive tests from the total of cases with disease, while specificity is derived as the percentage of all true negative tests from the total of cases with absence of disease. Sensitivity and specificity depend on the cut-off value used to define positive and negative test results (Obuchowski, 2003). Each point on the ROC chart is derived by using different cut-off values and the ROC curve is built from the set of all possible cut-off values (Obuchowski, 2003). The accuracy of the positive and negative classification of a diagnostic test, which can be termed true disease status, is estimated by standard ROC methods (Zou et al., 2007). The true disease status is named as gold standard (Zou et al., 2007). A gold standard is needed for identification of specificity and sensitivity of a test because any test can give incorrect results.

While sensitivity and specificity are measures of accuracy, predictive values are measures of performance (Schulzer, 1994). The predictive value of a test is a measure of how often the test result (positive or negative) is correct, i.e. the proportion of all positive tests that are true positives is the positive predictive value (PPV) and the proportion of all negative tests that are true negatives is the negative predictive value (NPV) (Schulzer, 1994; Zweig and Campbell, 1993). For such a test:

$$Positive\ predictive\ value = True\ positive/(True\ positive + False\ positive)$$
$$Negative\ predictive\ value = True\ negative/(True\ negative + False\ negative)$$

The PPV and NPV are dependent on disease prevalence in the studied population. They are affected by the prevalence differently: the PPV increases with increasing prevalence, while NPV decreases (Schulzer, 1994; Zweig and Campbell, 1993).

The ROC methodology provides an opportunity of identifying an optimum reporting cut-off value by identifying the point on the curve at which the sum of sensitivity and specificity is maximized (Zweig and Campbell, 1993). An ROC curve is a graphical representation of the sensitivity (true positive rate (TPR)) as the y coordinates versus $1-$specificity (the true negative rate (TNR)) as the x coordinates (Park et al., 2004) of a diagnostic test across a variety of possible test thresholds. A good model performance (Fig. 1) is characterised by a curve that maximizes the sensitivity for low values of $1-$specificity, where the ROC curve passes close to the upper left corner of the plot (Robertson et al., 1983; Schulzer, 1994). The diagonal line $y = x$ (Fawcett, 2006) is the ROC curve corresponding to an uninformative test that is no better than a random guess (see Fig. 1). The area under the curve (AUC) is a global (i.e. based on all possible cut-off values) summary statistic of diagnostic accuracy (Greiner et al., 2000). The possible range of the AUC is from zero to one. The uninformative test gives 0.5, and below 0.5 means worse