Interventions to manage Salmon Rickettsial Septicaemia (SRS) and Caligus infestation in farmed salmonid fish in Chile: design of a controlled trial

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PROGRAMA PARA LA GESTIÓN SANITARIA EN LA ACUICULTURA

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INTRODUCTION

Salmon Rickettsial Septicaemia and Caligus infestation are two of the most economically important diseases of salmonid fish farmed in marine waters of Chile. Measures to control these diseases add significantly to the costs of production and have been the focus of research efforts in Chile for many years. However, many interventions used to date have not shown marked or sustainable benefits.

A controlled trial is one option for a prospective study to evaluate new interventions. It will be considered in the context of the Sernapesca Disease Platform: a broader program of work to enhance knowledge about risk factors and evaluate novel interventions to control diseases of Chile's salmonid fish industries.

This section of the report outlines the prerequisites and approach to a randomised control trial. It is not a detailed study design, but is intended as background to support discussion about the type of prospective study that is most suitable.

OVERVIEW OF A CONTROLLED TRIAL

Controlled trials (interventions studies) aim to measure the effect of the intervention on predetermined outcomes. They are experimental (rather than observational) studies in which the investigator determines which study participants are exposed to the intervention and which are not; for example, the investigator would allocate some farms to the treatment group and others to a control group.

The objectives of the trial should be stated clearly in the study protocol, with reference to the intervention and the primary outcome to be measured, for example: to examine whether a specified treatment protocol using lufenuron is associated with a reduction in infestation with Caligus during a defined period of the production cycle. The trial would be designed to demonstrate superiority—i.e. a clinically important difference between the treated and control groups—under 'real world' conditions.

Controlled trials are considered to yield a very high level of evidence of causal associations, but they may be expensive to conduct and may not be practical or acceptable in some situations.

Separate controlled trials would be established for each of the interventions of interest, although these would be integrated as part of an overarching study. An outline of the approach is provided in the following sections.

PREREQUISITES

There are several essential conditions (prerequisites) for a controlled trial:

1. The investigator can randomly allocate farms (or cages) to treatment and control groups.
2. A adequately sized study population exists, consisting of farms that volunteer to participate in the study and are (preferably) representative of the broader target population.
3. It is possible and acceptable to administer the intervention in a commercial setting.
4. Sufficient resources are available to provide the interventions (and an alternative intervention to control groups) and make the necessary measurements on outcomes.
5. There is sufficient time to design and plan the study, including to apply for ethics approval (if required) recruit study participants.

If these conditions cannot be met, then an alternative type of study design (such as a cohort study) should be considered.

STUDY POPULATION AND SAMPLING METHODS

The geographical extent of the study, selection of barrios and the identification of farms eligible for inclusion in the study will be determined in consultation with government and industry partners. It will be important to consider the issue of generalisability—is the study population representative of a broader reference population of interest?

It may be necessary to define eligibility criteria (i.e. specific criteria for inclusion and/or exclusion from the study) for example, farms that are free from disease/infestation from barrios that typically experience high rates of infection/infestation.

As with the cohort study, further discussion is required to determine the appropriate unit of concern: the sea-cage or the farm.

Appropriate sample sizes will be determined after considering to both statistical factors (for example, Type I and Type II errors) and non-statistical factors such as the availability of resources. The study should have sufficient power to have a high chance of detecting a clinically (and perhaps economically) meaningful difference between treated and untreated groups. To calculate sample sizes, it is necessary to:

- Define the outcome measurements (for example, the sample size required for dichotomous outcomes is larger than that that required for outcomes measured on a continuous scale)
- Estimate the likely losses of study participants during the study period (for example, through non-compliance)
- Define a confidence level (acceptable level of Type 1 error)
- Decide on the desired power to detect a difference of a defined magnitude

- Decide on the magnitude of treatment effect (for example, difference in proportions, means or time-to-event)
- Estimate the variability in the treatment effect for treatment groups.

TREATMENT GROUPS AND RANDOMISATION

The way study participants are allocated to treatment groups would depend on the number of treatments included in the study; i.e. the number of 'arms' in the trial. For example, a 'two-arm' trial might compare a group treated with lufenuron with a group treated with an alternative drug. In a simple parallel design, participants are allocated to one of two or more treatment groups, the treatments are applied concurrently (in parallel) and outcomes are compared between the treatment groups.

Alternatively, a factorial design might be appropriate if we are interested in assessing the effectiveness of two or more treatments, given individually and in combination. In a factorial design, various combinations of the treatments are assigned to the study participants. This design is particularly useful if we are interested in the additive effect or if there are interactions between the treatments.

In all cases, it will necessary to determine what the other treatment groups are given; for example, an alternative treatment or no treatment.

Randomisation with sufficient sample size offers the greatest opportunity to create exposed and unexposed groups that are similar with respect to all other factors (including potential confounders), with the corresponding opportunity to isolate the effects of the intervention. Once eligible farms are selected for inclusion in the study, randomisation is used to ensure that the two groups are comparable: chance alone dictates which group each cage (or farm) is allocated to.

BASELINE MEASUREMENTS

Randomisation should ensure comparability of groups, but baseline data on outcomes of interest and other variable of interest (including potential confounders) should be collected to ensure that this has been achieved, and to allow control of confounding in the analysis. Baseline data should be collected before random allocation, so data cannot be influenced by prior knowledge of treatment group.

As for the cohort study, the literature review and consultation with collaborators will be used to identify and describe the variables (including management and environmental factors) that should be measured.

OUTCOME MEASUREMENTS AND BLINDING

Methods and frequency of measurement will be determined after the literature review and further consultation with collaborators: it will be important to measure outcomes and other variables as accurately as possible, given available methods and resources. It is possible that several outcomes could be measured; for example, development of severe Caligus infestations and Caligus prevalence each month.

If practical to do so, blinding should occur so that the people responsible for measuring outcomes remain unaware of which group (treatment or control) the farm belongs to.

ANALYSIS

Analysis of the data would include initial exploratory analysis to detect any data errors and provide a general description of the data. More complex statistical analysis would follow to test hypotheses.

Analysis includes a comparison of risk or rate of disease outcome, or difference in means or time-to-event, in the different treatment groups. Methods include crude comparison of risks or rates, estimation of vaccine efficacy, and survival analysis. Adjusted analysis with general linear models might be possible.

Adjustment of confounders is often unnecessary (random allocation should give rise to comparable groups), but analysis of baseline data is recommended to ensure comparability. If necessary, additional analysis should be conducted to adjust for other variables that differ between groups.

Primary analysis should be on an intention-to-treat basis; i.e. the overall effect of assigning a farm to a particular treatment group, irrespective of whether the treatment protocol was actually followed.

INTERPRETATION

The principal output from statistical models in controlled trials is the regression coefficient (β) that represents the amount of change in the outcome for every unit increase in the exposure (predictor) variable, having controlled for the effects of other variables in the model. Depending on the nature of the of data and type of analysis, these coefficients are usually converted to a more meaningful measure such as an odds ratio (in the case of logistic regression) or incidence rate (Poisson regression). The value of these coefficients then needs to be interpreted with consideration to possible sources of biases in a controlled trial:

Interpretation of results will need to consider possible sources of bias:

- Was randomisation effective?
- Were the treatment groups similar at baseline?
- To what extent was blinding achieved?
- Is there likely to bias in the measurement or recording of outcomes?
- What proportion of the farms were successfully followed up?
- What was the level of compliance with the interventions?

PRACTICAL CONSIDERATIONS

Costs

Controlled trials may be expensive to conduct, particularly if we are interested in evaluating several interventions. Given that the investigator assigns study participants to different treatment groups, study participants may expect the investigators to pay for whatever treatment is assigned to them. In a commercial setting where the treatments and associated management costs may be relatively expensive, the overall cost of the study might be prohibitive. In addition, producers may expect to be compensated for production losses associated with being assigned to a group where no treatment is given or where a level of treatment below what they would usually administer is given.

Time to recruit

Controlled trials depend on voluntary participation of a sufficiently large number of subjects (farms or cages) that are representative of the target population. It takes time and resources to recruit participants and—in a production context—allow sufficient time for farms to prepare for their participation in the study.

Ethics and acceptability

Controlled trials usually have to be approved by an ethics committee. Ethics committees evaluate factors such as the scientific justification for the study, whether appropriate steps will be taken to ensure informed consent of participants, and whether any animal welfare concerns might arise. The process of approval through ethics committees can take some time.

ADVANTAGES AND DISADVANTAGES

There are several **advantages** to a controlled trial in this situation:

- Likely to require a smaller sample size than an equivalent cohort study
- Investigators have control over the interventions, so they can ensure that there is appropriate contrast between treatment and control groups
- Randomisation is an effective way to control confounding (including known and unknown or unmeasurable variables)
- Clear temporal sequence between exposure and outcome
- Best evidence of causation

However, there are **some potential limitations and disadvantages:**

- Poor efficiency if outcomes are rare during the study period
- The investigators may not be able to influence the use of vaccines, treatments and selection of genetic stock on the farms of interest
- There may be some legal issues if the investigators are controlling (rather than simply observing) the way in which vaccines and treatments are administered in a commercial setting
- It may be expensive and time-consuming to conduct the study.

In addition, there are some **ethical considerations:**

- Controlled trials require informed consent: this is particularly important when the extent of the effects of the intervention is unknown.

As an alternative, a cross-over trial could be used, where each farm receives both the intervention and the control, separated by a 'wash-out' period, with the order of administration being randomised. However, this would have to occur over several production cycles and other variables (including environmental variables that can't be controlled) may vary over time, leading to difficulties in making valid comparisons.


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