Transfer of pathogens between farmed and wild aquatic animals – epidemiological basis for demonstrating causality

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Introduction

The rapid global expansion of aquaculture over the last 3 decades has resulted in large numbers of farmed animals being placed in close proximity to wild populations. This expansion has been accompanied by a rapid increase in the awareness of many aquatic animal diseases.

While there may be many reasons for a disease event, when farmed and wild fish are present and one or both populations are affected by the disease, a common hypothesis is that the disease has been transferred from one population to the other. Typically, farmers may suspect that disease in farmed fish is caused by contact with wild populations, while environmentalists may be concerned that disease in wild populations is a result of the presence of aquaculture.

This paper discusses the epidemiological basis of the establishment of causation, initially in the general context of animal diseases. It then considers the special case of establishing causation for pathogen transfer between farmed and wild populations, and provides guidance for surveillance activities that may provide evidence to support claims of causation.

Philosophical foundation

In the context of pathogen exchange, we are proposing a hypothesis that disease in one population has caused disease in a second population (or some variation on that theme). It is widely accepted that it is not possible to conclusively prove a hypothesis to be correct. It is possible to make any number of observations that are consistent with a hypothesis, each of which progressively lends further support to the idea. However, it takes just a single observation which is inconsistent with the predictions of the hypothesis to prove that it is wrong (Popper's concept of *falsifiability*).

If we are not able to prove any theory, how is it then possible to determine causation? In short, it is not possible. However, it is possible to examine theories, and through the use of a combination of empirical data and shaping principles, select better theories and progressively increase our confidence that they are, in fact, correct.

Shaping Principles

Shaping principles are non-empirical assumptions and factors, generally based on logic, that are used to help evaluate theories. The development of a set of shaping principles to guide evaluation of theories of disease causation was started by Robert Koch and his former professor Joseph Henle with the four Henle-Koch postulates (Koch, 1882). Sir Austin Bradford Hill (1965) formulated a new list of postulates, which was later refined by Evans (1975). These shaping principles are widely accepted guidelines for evaluating evidence of causation in epidemiology and may be summarised as: strength of association; consistency of association; specificity of association; temporality; biological gradient; plausibility; coherence; experimental evidence; and analogy. To this list is often added response to intervention.

Significance of Pathogen Exchange

It is common sense to assume that, where either no barriers or permeable barriers exist between wild and farmed populations (and species susceptible to a particular pathogen exist in both populations) that there is the opportunity for pathogens to be exchanged. The purpose of studies into pathogen exchange is therefore not to determine whether such exchange occurs (it would be

unusual and surprising if it did not occur in particular circumstances). Instead it is to determine if significant pathogen exchange occurs. A range of outcomes are possible, creating a wide scale of grey between the white of 'no impact' and the black of 'widespread mortality'. It is therefore first necessary to define the level of impact that is considered to be significant. Decisions about what level of impact are judged to be significant should be made taking the full range of considerations into account, including economic, environmental, social, political and biological.

Issues of Scale

Scale is a particular example of the difficulties in establishing the definition for significant impact. Consider the example of exchange of pathogens from a farmed population to a wild population of a relatively static species such as oysters. If one were to examine a population of wild oysters situated very close to farmed oysters, one may find a high prevalence of disease, and judge this to be a significant impact. However, examination of oysters somewhat further removed may reveal little or no impact. The assessment of impact is therefore dependent on the scale at which one examines the populations.

Unit of interest

In the case of pathogen transfer between farmed and wild populations, the unit of interest is the population rather than the individual, and this poses some very significant challenges. The first is the definition of a population. This may vary depending on the hypothesised direction of transfer of the pathogen. If it is considered that pathogens may have moved from farmed to wild populations, it is necessary to identify a number of (preferably discrete) populations of wild fish, some of which can be classified as 'exposed' (ie, have come into contact with farmed populations) and some of which are non-exposed. Definition of discrete populations of farmed fish, where transfers are suspected to be from wild to farmed populations may be easier (for instance a cage). However, there may be significant challenges in differentiating farmed populations that have been exposed to diseased wild populations and those which have not.

The second challenge is obtaining a 'population of populations', or an adequate sample size to achieve meaningful results in the study. In contrast to traditional studies designed to establish causation, where the unit of interest is the individual, when studying pathogen exchange, each population studied provides a single data point.

A third question relates to the assessment of the status of a population. Diagnostic tests are used at the individual animal level to determine if disease or a pathogenic agent is present or not. The same types of tests can be used at a population level, but it is rare that the entire population can be tested. Instead sampling approaches must be used, applying diagnostic tests of imperfect sensitivity and specificity, in order to make probabilistic statements about the status of the population. Definition of the assumed level disease that our population-level diagnostic procedure is able to detect (known as the design prevalence) is an essential part of classifying populations.

Application of traditional factors for causation

Strength of Association: Strength of association is one of the few shaping principles that can be measured quantitatively and is therefore important when investigating causation. When the unit of interest is the population, there are often significant practical challenges, related to defining populations, classifying populations as exposed or unexposed, as well as achieving an adequate number of observations (independent populations) to achieve meaningful precision in the estimates of the relative risk or odds ratio.

Temporality: This is a critically important shaping principle as it is the only one which must be true if a causal relationship is present. A cause must always precede the effect. When assessing the impact of farmed fish on wild populations, this requires that the health status of both populations be determined *before* exposure takes place (e.g. before farmed fish are introduced)

Biological gradient: Literal consideration of a dose-response effect is not possible in the context of wild-farmed interactions, as the exposure is dichotomous (infected or non-infected populations). However a similar idea can be assessed by using distance as an analogy for dose.

Intervention: If the putative cause is either removed or its actions are neutralised, and this is associated with a decrease in the disease, this provides good evidence of causation. For instance, if a farmed population of salmon is treated to remove all sea lice, and there is a subsequent decrease in the level of infection of the nearby wild population, this may provide evidence for a causal relationship. However, there are many reasons why this effect may be seen in the absence of a causal relationship, or why no effect may be observed, even if the farmed fish were the original cause of the infection in the wild population.

Of the 10 shaping principles, the most relevant to the issue of pathogen exchange between farmed and wild populations are: strength of association, consistency of temporal association, presence of a biological gradient, experimental evidence, and response to intervention. Plausibility, coherence and analogy are probably the weakest shaping principles in the Evans-Hill list, and can often be taken for granted in the context of farmed-wild pathogen exchange.

There are also a number of novel sources of evidence, not included in other published lists, which may be used to support an argument of causation. One of the key proposals of this paper is that, rather than being limited by existing lists of shaping principles, researchers should develop their own list of sources of evidence, applicable to their specific context. Such a list may be based on the work of previous authors, but inappropriate elements should be discarded, and novel approaches embraced. Examples of two such sources of evidence are:

Molecular tools: Pathogen exchange means that pathogens from one population have been transferred to another population. If the genetic make-up of pathogens in one population is identical to those in the other population, this is consistent with recent transfer having occurred. However if they are significantly different, it is unlikely that the different pathogens in the two populations were originally (and recently) derived from a single population decreasing the likelihood of transfer having occurred.

Serial sampling of naïve populations: An indication of the temporal relationship between exposure to a putative cause and development of disease (at the population level) may be determined when known uninfected animals are introduced into a population.

Conclusion

Sources of evidence to support claims of causation are largely qualitative, and therefore some subjectivity is inevitable. Demonstration of pathogen transfer between farmed and wild animals poses some significant challenges. These can be addressed, in part by the use of non-traditional shaping principles (such as molecular tools or serial sampling), careful forethought (to assist in gathering evidence on temporal relationships), and the accumulation of evidence from multiple sources.

References

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