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Strategies for Control of Nanophyetus salmincola *Parasites in the Pacific Northwest*

1. Abstract

Nanophyetus salmincola is a prevalent trematode in the northwestern United States which has pronounced pathology in salmonid fishes and domestic dogs. Current strategies for control of this parasite are minimal, consisting only of education campaigns designed to prevent transmissions in humans and dogs only. This ignores the significant effect that this parasite has on populations of juvenile salmon by greatly effecting their chances of survival. In order to control this parasite, several methods can be employed. From observing model cases of schistosomiasis control, I assess the possibilities for control of *N. salmincola*. These include continued education campaigns for reducing human and canine transmission, water treatment using formalin to protect salmon populations, use of molluscicides to kill the first intermediate host (the *Juga plicifera* stream snail), biological control using the introduction of a predator to control the snail intermediate host, or using interspecific competition between trematodes in the snail host to reduce transmission of *N. salmincola*. My recommendation is to begin water treatment in aquaculture and salmon enhancement facilities and supplement with molluscicide treatment in areas of high *Juga* spp. population. Utilizing the more novel biological control methods will require identifying either a potential predator for *J. plicifera* or a beneficial trematode to act as a competitor for *N. salmincola.* The risks for these methods will need careful assessment, but the potential benefits in terms of effectiveness and cost make further research into these methods a good idea.

2. Introduction

Parasitic worms are not a thing many people like to think about, but they are present all around us. In fact, in 2000 almost 50% of known animal species could be classified as parasites, and parasitism has evolved independently at least 60 times across evolutionary history (Poulin and Morand 2000). Some parasites can infect many different kinds of vertebrates for their final definitive host, and many of these less "picky" parasites are also able to infect humans- or more importantly, our furry friends. *Nanophyetus salmincola* is a parasite that uses mammalian definitive hosts, including but not limited to skunks, raccoons, dogs, and even humans (Schlegel et al. 1968). For most of these creatures, infection is largely harmless. But for the domestic dog, *N. salmincola* infection is often fatal if left untreated. (Headley et al. 2011) This is because *N. salmincola* harbors a dangerous parasite of its own, the bacterium *Neorickettsia helminthoeca* (Headley et al. 2011). When *N. salmincola* infects a dog, *N. helminthoeca* accompanies the trematode and infects the dog as well, resulting in an 90% fatality rate for the dog unless it is treated within 6-10 days of symptoms (Headley et al. 2011). In addition to the infections in humans and pets, *N. salmincola* uses salmonid fishes as an intermediate host, with harmful effects on the population of salmon (Jacobson et al. 2008) that already experience substantial threats to their future existence.

In this report, I will discuss the current pathology and treatment methods, summarize and assess the current methods for controlling *N. salmincola* distribution, and suggest a novel method of control for the parasite in the hope of preventing cases of so-called "salmon poisoning" in domestic dogs as well as lessening the burden on endangered salmon populations.

3. *Nanophyetus salmincola*: Basic Facts

Nanophyetus salmincola belongs to the class Trematoda, phylum Platyhelminthes. Trematodes include such notorious members as *Schistosoma mansoni, haematobium, and japonicum*- known for human infections of Schistosomiasis- and *Fasciola hepatica/gigantica*, more commonly known as the liver fluke.

Nanophyetus salmincola has a life cycle similar to that of other trematodes, with a first intermediate snail host, a second intermediate fish host, and a definitive vertebrate host. The adult worms of *N. salmincola* live, sexually reproduce, and produce eggs in the definitive host's upper small intestine (Bennington and Pratt 1960). These eggs are expelled in the host's feces and hatch into miracidia if they end up in fresh water. The miracidia can swim in water and make their way into a snail host (*Juga plicifera*) by penetrating their body cavity and nesting in the snail's gonads (Bennington and Pratt 1960). Miracidia develop into rediae, which asexually reproduce to create more rediae (Bennington and Pratt 1960). Once a sizable colony has formed inside the snail, the rediae begin producing cercariae, which leave the host snail to seek the second intermediate host (Bennington and Pratt 1960). This is usually a salmonid fish, though other kinds of fish have been reported to host *N. salmincola* (Bennington and Pratt 1960). The cercariae penetrate the fish and encyst themselves in the host's tissues, turning themselves into metacercariae (Bennington and Pratt 1960). For *N. salmincola*, most metacercariae can be found encysted on the kidney of the fish (Jacobson et al. 2008). When the fish containing the metacercariae are consumed by the definitive mammalian host, they excyst themselves and finish developing into adult flukes, ready to repeat the cycle (Bennington and Pratt 1960).

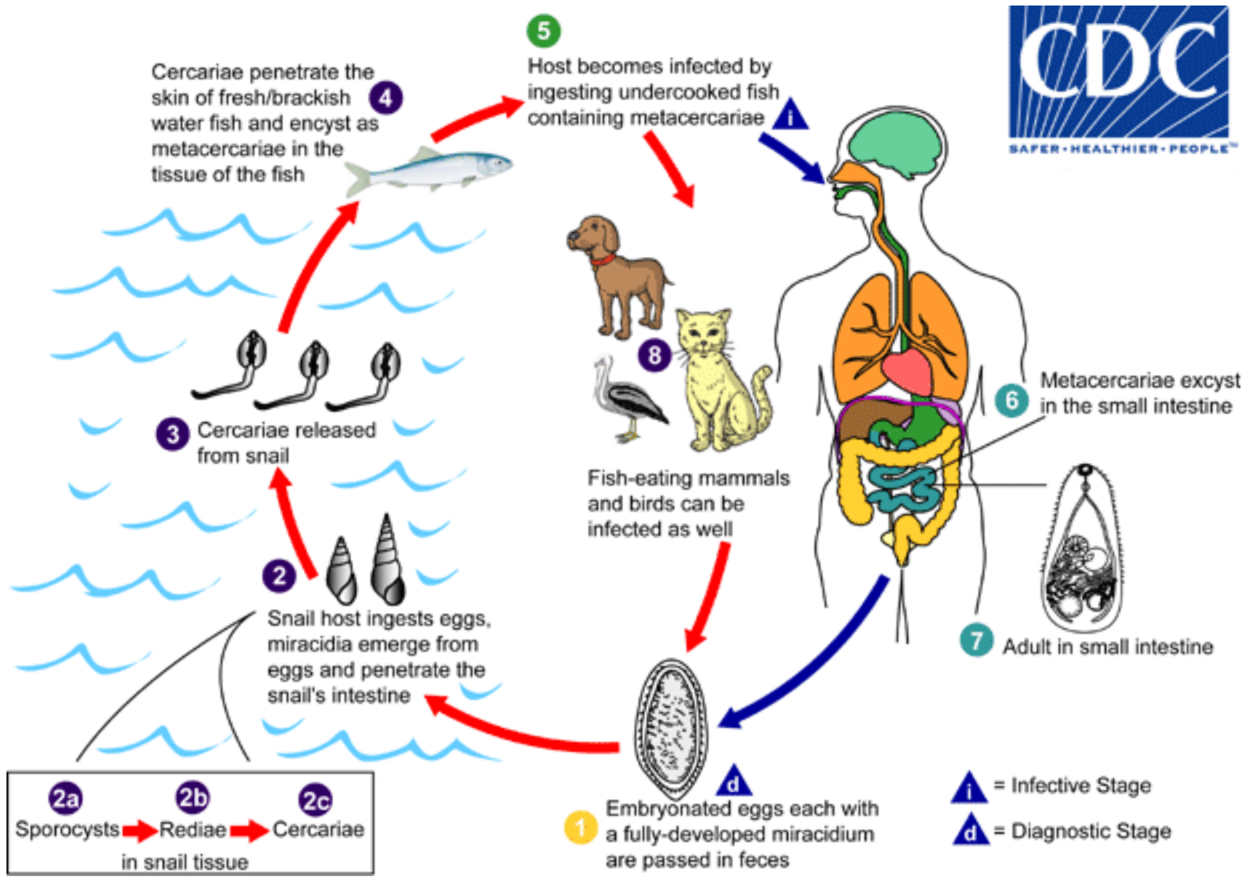

Figure 1: Diagram of a trematode (*Heterophyes* spp.) life cycle similar to that of *Nanophyetus salmincola*. Notable differences include that *N. salmincola* is not known to infect birds and that its eggs hatch in water, with miracidia actively seeking the snail host and penetrating it rather than waiting for trophic transmission. Reprinted from U.S. Center for Disease Control DPDx website. 2018. Retrieved December 10, 2020 from https://www.cdc.gov/dpdx/heterophyiasis/index.html.

3.1 Pathology in Mammalian Definitive Hosts

N. salmincola is capable of infecting numerous mammals, including humans, dogs, racoons, skunks, weasels, and others (Schlegel et al. 1968). Pathology for most definitive hosts is dependent on the intensity of the infection and revolves around the inflammation of the intestinal cells surrounding the area that the trematode attaches to (Fritsche et al. 1989). Most patients tend to be asymptomatic or have mild symptoms of infection- abdominal pain, diarrhea, gas and bloating, and eosinophilia (Fritsche et al. 1989). Humans are generally treated with Praziquantel (Fritsche et al. 1989), a drug commonly used for deworming other trematodes as well (Chai and Jung 2020). Dogs can be treated with Praziquantel as well, but have also been treated with chloramphenicol (Booth et al. 1984).

3.2 Pathology in Salmonid Intermediate Hosts

For the second intermediate host, the salmonid fish, high exposure to *N. salmincola* cercariae can result in death due to trauma from the penetration process (Bennington and Pratt, 1960), but even under normal exposure conditions the fish still suffer increased sensitivity to other infections (Roon et al. 2015) as well as reduced swimming ability (Butler and Millemann 1971) and lower chance of survival for juvenile fish (Jacobson et al. 2008) as the metacercariae encyst on various tissues of the fish. Jacobson et al. showed in 2008 that *N. salmincola* infections are a significant source of mortality for salmon in their early life stages and contribute to their overall burden.

3.3 *Neorickettsia helminthoeca*

The major problem for domestic dogs is that *N. salmincola* is itself host to a neorickettsial bacterium, *Neorickettsia helminthoeca* (Headley et al. 2011). This bacterium is released from the trematode via an unknown mechanism and quickly spreads through the circulatory system and lymph nodes, resulting in vomiting, weight loss, depression, dehydration, anorexia, and polydipsia (Headley et al. 2011). Enlarged cervical and pre-scapular lymph nodes can be seen five days after infection, and diarrhea begins containing increasing amounts of blood (Headley et al. 2011). Internal hemorrhage or rupture of the intestinal tract (peritonitis), gall bladder, and urinary bladder has also been described (Headley et al. 2011). This condition is referred to as

Salmon Poisoning Disease, or SPD, and is treatable using antibiotics such as oxytetracycline, deworming agents such as Praziquantel, and supportive therapy. (Headley et al. 2011).

3.4 Geographic Distribution

The distribution of *Nanophyetus salmincola* is closely tied to the distribution of its intermediate host snail, *Juga plicifera*, which is found in most freshwater streams and rivers west of the Cascade Mountains from northern California to the Olympic Peninsula in Washington (Eastburn et al. 1987) (Campbell et al. 2016). Snails in this region have a 9% to 52% incidence of infection, varying by time of year (Eastburn et al. 1987). The snails seem to prefer clear, running water such as permanent springs and streams to standing water and settle on hard substrates rather than sand or mud (Campbell et al. 2016).

4. Analysis of Control Methods

There is a vested interest in controlling this trematode from several angles. First is the emotional aspect of its high lethality in dogs, which are often beloved pets in the United States. Secondly is the potential health risk for humans- while *Nanophyetus salmincola* is not generally lethal in humans and *Neorickettsia helminthoeca* has not been reported to infect humans, the zoonotic potentials of this bacterium and others that infect *N. salmincola* are not fully understood. Multiple species of *Neorickettsia* have been known to infect *N. salmincola* which produce SPD-like effects in other mammals including bears (Greiman et al. 2016), which is a concerning discovery from a zoonosis standpoint. Thirdly, and potentially most importantly, salmon populations in the northeast Pacific are heavily impacted by *N. salmincola* in their younger life stages, with many fry killed by *N. salmincola* cercariae when salmon spawn in freshwater streams (Jacobson et al. 2008). Salmon are already under high pressure from fishing and environmental changes and eliminating a source of early-life burden may help to bolster salmon populations, especially since these populations are projected to have increased risks in the future (Landis 2020). With each of these goals in mind, a fair amount of research has occurred both for *N. salmincola*-and other trematodes that can serve as model cases- which allow us to get insight as to potential management strategies for *N. salmincola*.

4.1 Current Control Methods

The main method of transmission for *N. salmincola* in humans and dogs alike is the consumption of undercooked fish. This is especially common in the dogs of fisherman, who are often fed the offal or other unused pieces of someone's infected catch, unintentionally transmitting the parasite through the pooch's treat. Currently the only control method for *N. salmincola* is post-infection treatment and public health campaigns urging people to avoid eating improperly cooked fish or feeding improperly cooked fish to their pets. Research thus far has focused more on the effects of *N. salmincola* on salmon populations, and potential new control methods that can arise from that research.

4.2 Water Treatment

Formalin and seawater are both proven to kill waterborne *Nanophyetus salmincola* cercariae under lab conditions, as well as high doses of hydrogen peroxide (Hershberger et al. 2018). The inability of *N. salmincola* cercariae to survive higher salinity in water is notable, since this means exposure to fish must be occurring only in freshwater (Hershberger et al. 2018). These findings are recent, and chemical treatment for *N. salmincola* has not yet been attempted. However, it is my opinion that a chemical treatment plan would not be able to eradicate the parasite nor assist substantially in preventing transmission to wild salmon, as these fish are also incapable of surviving in formalin or hydrogen peroxide and require freshwater to spawn. In closed-off aquaculture facilities and salmonid enhancement facilities these treatments could be substantially effective in preventing transmission, provided such facilities are also taking other precautions against the parasite such as avoiding sites with high abundance of *Juga plicifera* (Hershberger et al. 2018).

4.3 Controls for *Schistosoma* spp. as Model Cases

There are several related trematode species that are considered a higher priority for control than *Nanophyetus salmincola*, including the infamous *Schistosoma* spp. These blood flukes have a much higher prevalence in human populations and are more debilitating, necessitating the development of several treatment strategies that can be used as model cases for *N. salmincola* due to their similar life cycles and biology, with the caveat that *Schistoma* spp. do not have secondary intermediate hosts- their cercariae can directly infect people rather than requiring trophic transmission (Nelwan 2019).

The primary method of control for schistosomiasis- the condition caused by infection with parasites of *Schistosoma* spp.- is to treat at-risk communities using Praziquantel several times throughout the year, periodically killing off all schistosomes present in the population (Inobaya et al. 2014). This is done with the goal of preventing them from producing any eggs and eventually eradicating them. The problem with applying this control method to N*anophyetus salmincola* is that *N. salmincola* does not use humans as its largest reservoir- rather, infection is much more common in other wild mammals that live near water such as raccoons and skunks (Schlegel et al. 1968). Additionally, the prevalence of infection in the United States is not high enough to justify mandatory treatments on a logistical level, with only around 20 cases reported in literature between 1974 and 1987 (Eastburn et al. 1987) (Chai & Jung 2020).

The secondary method of schistosome control which is often applied in combination with periodic chemotherapy is snail control. Molluscicides are used in areas with high snail concentrations in order to kill the intermediate host of *Schistosoma* spp., thereby reducing the number of schistosome cercariae produced (Inobaya et al. 2014). Snail control could be a good method for limiting transmission of Nanophyetus salmincola. Reducing the number of cercariae in the water would decrease the intensity of infections for juvenile salmon, and fewer salmon infected would result in fewer mammalian hosts, reducing the number of *N. salmincola* eggs in the next generation. This cycle could lead to eradication of the parasite, but of course there are costs to this strategy. First is the physical cost of the chemicals and of hiring people to track down and apply molluscicide to all the concentrations of *Juga plicifera* in rivers that salmon also spawn in. Multiple doses of molluscicide are often needed to eliminate snails as well (Coura-Filho 1992), so this would also be a multiplying factor to the amount of effort people are willing to spend to eliminate this parasite (Inobaya et al. 2014). Secondly, placing molluscicide in the water could result in further environmental damage, such as killing off fish or other organisms (McCullough 1992). Over time, snails can develop resistance to molluscicides as well, reducing effectiveness and requiring the development of new molluscicides or the application of multiple chemicals at the same time (Coelho and Caldeira 2016).

4.4 Theoretical Methods of Control

There are a handful of control strategies that are only loosely based on existing research and would need additional information and experiments in order to determine their feasibility. Both are biological control options, involving the introduction of another organism to control *Nanophyetus salmincola*.

The first potential method I propose would be the introduction of a predator for *Juga plicifera*. In a study in Kenya in 1999, invasive *Procambarus clarkii* crayfish were shown to reduce schistosomiasis re-infection rates by hunting intermediate host snails (Mkoji et al. 1999). These crayfish established very quickly in their new habitat despite their small initial numbers, and both the number of snails and the number of re-infections among children in a nearby school dropped significantly. This strategy has a few notable qualities- it is effective at reducing transmission of the parasite quickly, it would be much cheaper to perform than periodic molluscicide doses or pre-emptive Praziquantel treatments, and it involves little direct human activity. On the other hand, introducing invasive species as a biological control has a poor track record, and unintentional ecological effects are sure to result from introducing a new snail predator that has no control of its own. In the specific case of *N. salmincola* and *J. plicifera*, a good candidate predator would also need to be identified before such a strategy could be implemented. This necessitates further studies on the ecological role of *J. plicifera* and experimental treatments to see if any invasive snail predators will target it.

The second potential method of control exploits a strange quirk of the trematode life cycle which bears explaining first. In the snail intermediate host of most trematodes, the miracidia develop into rediae, which live colonially in the snail host and produce cercariae. However, according to Hechinger et al. in 2011, rediae exhibit two morphs that acts as a "soldier caste" and a "reproductive caste" within the colony. Some rediae are large, mostly immobile, and do little except produce cercariae (Hechinger et al. 2011). Other rediae are small, mobile, and possess large mouthparts that they use to fend off threats to the reproductive rediae, including other trematodes (Joe 1966). These findings suggest that it may be possible to infect *Juga plicifera* with a different, less harmful trematode, which can then outcompete *N. salmincola* and prevent it from infecting new snail hosts. One potential candidate could be *Metagonimoides oregonensis*, a trematode which uses *Juga spp*. snails as the first intermediate host in the western United States and uses amphibians as a second intermediate host and small mammals as definitive hosts (Belden et al. 2012). This strategy has never been tested in *Nanophyetus salmincola* but if a "beneficial trematode" can successfully fight off *N. salmincola* while not spreading to human and canine hosts, it would certainly be an elegant solution to the problem. In *Schistosoma mansoni*, competition over snail hosts with other trematode species such as *Calicophoron sukari* resulted in a reduction of transmission to human hosts for *S. mansoni* (Laidemitt et al. 2019), which shows that a similar strategy for *N. salmincola* control is possible should a suitably antagonistic trematode be found. It would solve the problem of *N. salmincola* infection and Salmon Poisoning Disease while preserving the snails themselves to maintain the current food chain and minimize ecological harm. Much more research would need to be performed in order for this to happen, including experiments on whether trematode colonies are really capable of such an "immune response" against other trematodes, or if the study merely caught an edge case. Additionally, a candidate trematode species to replace *N. salmincola* would need to be identified and scrutinized for its ecological impact to ensure we don't introduce new problems.

5. Recommendations for *N. salmincola* Control

With the past methods of control in trematodes in mind, it seems apparent that more research would be required in order to accurately determine the impact of applying these strategies to *N. salmincola.* The current method of control is to minimize transmission to humans and dogs through providing information about the parasite's mechanism of transmission. Expanding such education programs would be a good first measure to take in controlling this parasite. However, it is also clear that this will not reduce rates of parasitism in salmonid fish, many of which are protected or endangered and would greatly benefit from reduced parasite burden. Wild reservoirs are the primary place of transmission for this parasite which makes any strategy for complete eradication practically impossible. With that in mind, the best strategy analyzed here is likely the use of water treatment in salmonid enhancement facilities. The high degree of control for water input and monitoring of the salmonid population makes such places ideal for filtering *N. salmincola* cercariae from the water and preventing transmission to the fish populations. This wouldn't protect wild populations, so developing a method of treating water in a less controlled environment should become a research priority to determine what can be done. This would require a higher amount of funding, but it could greatly assist salmonid populations in avoiding becoming secondary hosts to *N. salmincola*, which would also lessen the burden of infection on the mammalian hosts who would otherwise become infected by eating the fish. Over time, this would reduce the number of *N. salmincola* and prove an effective control.

The present situation with schistosomiasis control also informs us that a variety of strategies working in concert is often more effective, so a good suggestion would be pairing water treatment with other methods of control. If a safe biological control based on one of the theoretical methods above could be found, this would be a highly effective way to augment an existing strategy to ensure that *N. salmincola* is greatly reduced in abundance. Otherwise, a molluscicide approach could be followed in areas with remarkably high concentrations of snails would also help to reduce parasite burden by reducing the maximum number of snails that can be infected. Applying molluscicides in advance of seasons when *N. salmincola* cercariae are most active, such as in advance of salmon spawning runs (MacKenzie et al. 2019) would likely be the most efficient strategy. The combination of several strategies would prove to be more effective than any individual plan.

To conclude this recommendation, it is clear that more research on the specifics of *N. salmincola* infection will be required to fully understand what methods of control would be the best. Plenty remains unknown; for example, what is the prevalence of *N. salmincola* in wild mammals? Which wild mammals are the most important reservoirs? What is the method by which *Neorickettsia helminthoeca* infects canid hosts? Why does *N. salmincola* host *N. helminthoeca*? If *N. salmincola* is to be controlled, experiments attempting to reduce *N. salmincola* abundance will need to be developed and carried out as trial runs for a future management strategy.

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