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***Cyprinid herpesvirus 3* and its relevance to human health**

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Executive Summary

What the report is about

This report summarises the findings of a systematic literature review that sought to determine the impact on human health of the proposed release of the carp herpesvirus, Cyprinid herpesvirus 3. The literature review indicated that there is no published evidence of a direct zoonotic risk to human health from the virus. There was little published on how humans react emotively to mass mortality events of fish, however it could be reasonably assumed that the public may react adversely to mass mortality events. Rapid removal of the dead fish will mitigate adverse reactions.

Background

In Australia, carp (*Cyprinus carpio*) has been considered an invasive pest species following importation of the Boolarra strain of carp in the 1960s and floods in the 1970s causing the movement from isolated farm dams into the Murray-Darling Basin catchment. Since the mid-2000s, an integrated carp control program has been in development, including using Cyprinid herpesvirus 3 (CyHV-3), a species of Herpesvirales, as a biological control agent.

Recently CyHV-3 has been proposed as a potential biological control method for carp in Australia. While there is evidence evaluating the susceptibility of non-target species, concern remains around the ecological and environment impact of the release of the virus.

Aims/objectives

This report aims to review the published literature to provide a risk assessment of the potential impact on human health from the release of the virus into Australian inland water systems. The report also aims to consider the psychosocial effects of a mass fish die off after the release of the virus in the context of similar events that have previously occurred.

Methodology

A standard literature review was conducted for the purposes of developing background information to lead into the systematic literature review. A systematic review of the literature was conducted to review the relevance of Cyprinid herpesvirus 3 to human health. Standard search strategies were employed to search literary databases including to MEDLINE, PubMed and Google Scholar. Reference lists of included studies were examined for additional potentially useful literature.

The systematic literature search data extraction process involved two persons contemporaneously searching databases using a combination of pre-agreed MeSH subject headings and key words. Discrepancies in the retrieved articles were discussed and resolved by the persons conducting the data extraction. The abstracts of the retrieved studies were screened to identify which papers met the inclusion criteria. Information was extracted from the selected papers for inclusion in the discussion paper.

Results/key findings

Overall, there was no identified published literature to support any direct risk to human health from the carp herpesvirus CyHV-3. There is no published evidence to indicate that the virus has or will develop zoonotic capability. There was very little in the published literature on the impact to human health of mass mortality events associated with carp. The main reported impacted on humans due to mass mortality events of fish were in terms of loss of income where the fish in question were a cash crop.

Recommendations

While there is little published on how humans react emotively to mass mortality events of carp or other fish, it could be reasonably expected that there is likely to be a public reaction to mass mortality events of carp should the virus be released into Australian inland waterways. It is recommended that any plans for release of the virus also include strategies for management of collection and disposal of the dead fish, together with a communication plan for the general public.

Keywords

Cyprinid herpesvirus 3; human health.

Introduction

In Australia, carp (*Cyprinus carpio*) has been considered an invasive pest species following importation of the Boolarra strain of carp in the 1960s and floods in the 1970s causing the movement from isolated farm dams into the Murray-Darling Basin catchment [1, 2]. Since the mid-2000s, an integrated carp control program has been in development, including using *Cyprinid herpesvirus 3* (CyHV-3), a species of *Herpesvirales*, as a biological control agent [1, 2].

Herpesvirales

Herpesvirales are an order of viruses with linear, double-stranded DNA and an icosahedral capsid structure [3]. Infection with these viruses can cause both lytic and latent infection in a wide variety of hosts including mammals, birds, fish, reptiles, amphibians, and oysters [4, 5]. They tend to be highly species specific viruses and, due to the genetic difference between groups of the virus, are divided into 3 families: *Herpesviridae*, *Malacoherpesviridae* and *Alloherpesviridae* [3-6].

Herpesviridae comprise more than 130 characterised viruses across 3 subfamilies that infect reptiles, birds, and mammals [5, 7]. Humans are host to 8 of the herpesviruses within this family [5, 8].

The *Malacoherpesviridae* family includes only 2 recognised herpesviruses that affect bivalve molluscs - the oyster herpesvirus OsHV-1 and the abalone herpesvirus AbHV-1 [9, 10].

The third family within *Herpesvirales*, *Alloherpesviridae*, is divided into 4 genera that infect fish and amphibians: *Batrachovirus*, *Cyprinivirus*, *Ictalurivirus*, and *Salmonivirus* [7]. A number of fish species are affected by these herpesviruses including catfish, carps, sturgeon, eel, and salmonid [7]. *Alloherpesviridae* can result in devastating disease and high mortality in fish populations, with symptoms including haemorrhaging, necrosis, dermatitis, hyperplasia, hypertrophy, and encephalitis [6]. Similar to other families of herpesviruses, *Alloherpesviridae* appear to cause disease only in one species of fish or in closely related members of the same genus [6]. This report will focus specifically on the *Alloherpesviridae* *Cyprinid herpesvirus 3*.

Cyprinid herpesvirus 3

CyHV-3, initially referred to as koi herpesvirus, is a highly contagious virus in the *Alloherpesviridae* family that affects koi and common carp [6, 11, 12]. It is one of the four species in the *Cyprinivirus* genus and is generally detected by cell culture, real-time PCR, nested-PCR, TaqMan PCR, or by capturing viral particles with antibodies followed by loop-mediated isothermal amplification (LAMP) [13-15]. CyHV-3 has a similar morphology to other *Herpesvirales*, with virions diameter of 167-200nm according to the infected cell [16]. Whole genome sequencing has shown that CyHV-3 has the largest recorded genome among the herpesviruses at 295 kb [13, 16].

Outbreaks of CyHV-3 in carp populations were first reported in Germany in 1997 and from the USA and Israel in 1998 [11]. Over the following years, CyHV-3 spread rapidly to other countries, likely due to a combination of factors including global movement of fish due to farming and ornamental trade and inadequate testing and control to prevent spread of the virus [11, 17]. By 2010, CyHV-3 had been identified in koi or common carp populations everywhere in the world except in Australia, northern Africa, and South America [14].

CyHV-3 has caused mass mortality in carp populations in a number of countries, with mortality rates up to 80-100% [2]. Horizontal transmission of the virus occurs rapidly and generally when water temperatures are between 18 and 28 degrees Celsius [2]. Direct transmission likely results from skin-to-skin contact between infected or carrier fish and non-infected fish, while fish droppings, plankton, sediments, aquatic invertebrates feeding by water filtration, and water are potential sources of indirect transmission [2]. The virus can remain asymptomatic in the carp body for long periods of time when temperature prevents virus replication, with new infection occurring following a change of water temperature to 18-28 degrees Celsius

[14]. CyHV-3 generally enters through the skin and then spreads through the bloodstream to the kidney and other organs [18]. While carp of all ages are susceptible to CyHV-3, juvenile fish (1-3 months, 2.5-6 grams) seem to be more affected than mature fish [14]. There is conflicting evidence about whether larvae (3 days post hatching) are susceptible to infection [2, 14].

Like with other *Herpesvirales*, infection can be latent or lytic [19]. Clinical signs are variable in individual fish and include lethargy, anorexia, folding of the dorsal fin, increased respiration, excess mucus production, uncoordinated swimming, hyperaemia, haemorrhaging on the skin, and necrosis of the gill and internal organs [2, 20]. The development of disease in carp is also variable, but clinical signs generally appear 2 to 3 days post infection and mortalities 6 to 8 days post infection [2, 18].

Due to the high mortality rate, CyHV-3 has been detrimental to the production of carp for food, resulted in financial and economic losses in the koi and common carp ornamental and farming industries. It is a recognised as an economically and sociologically important pathogen and is a disease notifiable to the World Organisation for Animal Health (OIE) and the European Union (EU) [14, 15, 21].

Recently CyHV-3 has been proposed as a potential biological control method for carp in Australia [22]. While there is evidence evaluating the susceptibility of non-target species [1], concern remains around the ecological and environment impact of the release of the virus [23]. This report aims to review the published literature to provide a risk assessment of the potential impact on human health from the release of the virus into Australian inland water systems. The report also aims to consider the psychosocial effects of a mass fish die off after the release of the virus in the context of similar events that have previously occurred.

Objectives

This project was undertaken at the National Centre for Epidemiology and Population Health (NCEPH) at the Australian National University for the Fisheries Research Development Corporation. This report provides an assessment based on the available published literature of the relevance to human health from the release of the *Cyprinid herpesvirus 3* into Australian inland water system. The relevance to human health includes: (1) risk of direct transmission and (2) impacts of mass mortality events.

Method

Background literature

A standard literature review was conducted for the purposes of developing background information to lead into the systematic literature review. A search of PubMed was conducted using the search terms: ("Cyprinid herpesvirus" OR "koi herpesvirus" OR "CyHV-3" OR "carp herpesvirus"). The search produced 264 publications of which the most relevant 50 were utilised for the background section of this report.

Zoonoses literature

An additional standard literature review was conducted to provide a summary analysis on zoonoses more generally. The initial search terms used in PubMed of ("zoonotic AND virus*") produced over 4000 references, most of which were on the topic of influenza viruses. Narrowing the search terms to: ("fish" AND "virus" AND "zoonoses" AND "health") reduced the list to 13, of which most were related to swine influenza viruses despite the restricted search terms. A more targeted search to obtain information relating to the zoonotic potential of CyHV-3 was conducted using the reference lists of the publications retrieved in the background literature search.

Systematic review of the relevance of CyHV-3 to humans

Using SuperSearch, a systematic review was conducted using the terms: (cyhv-3 OR cyprinid herpesvirus 3) AND ((ecolog* OR environ* OR human*) AND impact*). This combination of terms sought to find any publications that would reference CyHV-3 virus and its impact on either ecology, the environment or humans (including human health).

When the search terms were limited to the 'title' AND 'abstract' fields only of the SuperSearch, a total of zero papers were retrieved. When the search terms were limited only to the abstract field, a total of 4 papers were retrieved. When further expanded to include 'any field', a total of 186 items were retrieved.

The resulting literature from the search was evaluated by two persons, using the same exclusion/inclusion criteria, to identify which papers were of relevance. Exclusion criteria included papers of a biochemical nature or on genetics research. Selected papers were all in restricted to English language with the exception of one paper in French. Papers published in other languages were not included. A total of 16 papers were deemed sufficiently relevant, with a further six being of potential relevance. The search also uncovered nine further papers related to the background of the virus that had not been identified during the initial background literature search.

In comparison with SuperSearch, using the same search terms in PubMed produced 2 papers and using SCOPUS resulted in 8 papers being identified. These searches were clearly more specific in output but resulted in fewer useful papers being identified. Both of the PubMed papers were captured by the SuperSearch, and seven of the SCOPUS papers has also previously been identified. The eighth paper was new to the search, and was considered relevant. This highlights the imperfections of search strategies and the need to be flexible when searching unusual topics that do not neatly fit into expected combinations of MeSH search terms.

The reference lists of retrieved publications were scanned to identify other potentially useful publications.

Systematic review on mass mortality events and psychosocial impact on humans

A second SuperSearch was conducted using the terms: ("mass animal death*" OR "mass fish death*" OR "animal die-off" OR ("fish*die-off" OR "fish die off" OR "animal* die-off" OR "animal* die off") AND (psychosocial* OR trauma* OR impact*). This sought to identify the publications on reactions from people to mass mortality events in animals.

When the search terms were limited to 'Title' AND 'Abstract', a total of 19 papers or media articles were retrieved. Every item was on the topic of mass fish deaths due to pollution or other events, and primarily in Asian countries. When expanded to only 'Abstract', a total of 101 items were identified. When the terms were included for 'any field', 1569 items were retrieved. A quick scan indicated that most were not relevant, and hence for this search the results were taken from using the search terms in the 'Abstract' field.

As per the first SuperSearch of the literature, two persons sifted the resultant items with exclusion and inclusion criteria. A total of 31 papers and media articles were deemed sufficiently relevant. As per previously, the reference lists of retrieved publications were scanned to identify other potentially useful publications.

Further information is provided at Appendix 1 on the databases used for the literature searches and the systematic review process.

Results and Discussion

Zoonotic risk of CyHV-3 to humans

Overall, there was no identified literature to support any direct risk to human health from the carp herpesvirus CyHV-3. While some viruses have achieved the ability to transmit from animals to humans, and in some cases the ability to then transmit human to human, there is no evidence to suggest that the carp herpesvirus has this capability or will develop this ability. While the order of Herpesvirales does include several important human pathogens, including herpes simplex viruses 1 and 2 as well as Kaposi's sarcoma-associated herpesvirus, the three distinct groups of viruses that form the three family levels of classification within the order are considered to be 'only tenuously related to each other' [24, 25]. As per the updated taxonomy of the herpesviruses [3], Herpesviridae retains the viruses of mammals, birds and reptile; Alloherpesviridae incorporates fish and frog viruses; and Malacoherpesviridae contains a bivalve virus. Such taxonomic separation noting the grouping of host species would indicate it unlikely for the CyHV-3 virus to develop the ability to transmit to and create disease in humans. Further supporting this are the studies from McColl [26, 27] indicate high species-specificity, even with fish.

Further it is important to note the temperature permissive range of CyHV-3, that being the temperature range at which the virus can survive. For CyHV-3, the permissive temperature range is 18 to 28° C [28, 29]. Temperatures outside this range do not support growth of the virus. As such the virus cannot infect mammals which have body temperatures higher than 28° C.

CyHV-3, like many pathogens, is capable of infecting only a limited range of host organisms, that being carp and koi, but excluding humans. As such the transmission risk to CyHV-3 would appear to be less than negligible with there being no identified published evidence of a transmission risk to humans.

Environmental and ecological impacts and water-user concerns

Water-user concerns may relate to the risk of transmission but also the ecological and environment impact of the biomass of rotting fish as well as the visual impact resulting for a mass mortality event associated with carp. There was very little in the published literature or media on such events, although a few media items noted the importance of keeping beaches and waterways clean.

It is noted that there are possible concerns about impact of oxygen depletion due to MME of fish and rotting biomass. However, there was little in the literature on the impact of oxygen depletion in waterways as a result of a fish MME. It was instead reported for the the reverse; that is low oxygen levels in waterways leading to mass deaths of fish MME.

Psychosocial impact of mass mortality events

There is very little published in peer-reviewed journals on the topic of psychosocial impacts on humans of mass mortality events of animals. This is even true for those animals more readily anthropomorphised and more closely related to humans, such as whales and dolphins. The literature search retrieved a small number of papers on the subject, despite there being numerous events reported in the media and the published literature. Notably these papers were on the impact of death of a companion animal with which the human had an established relationship [30, 31].

While published studies have mapped the frequency, location and type of mass mortality events involving animals [32], there was little published on how people and populations respond or react to these events outside of concerns for animals of monetary value such as fish deaths affecting fisherman and herding animal deaths for shepherds [33, 34]. There was some concern reported in media articles regarding the possible increasing scale and frequency of the events, but this was more in the context of what this might signify in terms of global climate health [35-37].

The few media items on mass mortality events involving birds that were uncovered as part of the literature search reported people being distressed by the scenes of numerous injured and dying animals [38, 39]. The fact that the birds died in a visible urban environment likely added to the emotive reaction of the public. A lesser reaction could reasonably be expected for a similar event in a remote location out of the public eye.

The main reported reaction of humans to MME specifically involving fish is in terms of reaction to loss of income where the fish in question are a cash crop. MME involving fish were more likely to report on impact on the income of fisherman rather than any other impact. That is, any published aspects of ecology and environment were with regard to causality of the MME, rather than on what effect the MME might have on the environment due to biomass of dead fish.

It is reasonable to assume that children may experience distress when observing mass fish die-off events. However, no published literature was retrieved on this specific topic, with the most similar published material being on children's reactions to death of a companion animal.

Mass mortality events of carp and koi

The common carp, *Cyprinus carpio*, are an important food fish in some parts of the world. *C. carpio koi*, a subspecies of the common carp, are a popular ornamental fish. These fish have been extensively cultivated and transported and are now distributed throughout the world. Both fish are susceptible to CyHV-3.

Mass mortality events relating to CyHV-3 have been reported in numerous countries. The virus was first described in Israel and the USA in 1998 [40]. Since the first isolation of the virus, KHV has been found to have a nearly widespread distribution. It has been the causative agent for mortalities among common carp and koi in many countries in Europe as well as in South Africa, Asia, the USA and Canada [17, 28]. The extensive spread of the virus has been thought to be due to various factors including global trade in ornamental and aquarium fish, historic short-comings in diagnostic methods and lack of legislation to control and prevent incursion of the virus [17].

In terms of biomass and ecological impact of mass mortality events of carp, accounts from events from other countries are useful in understanding the context of what might occur in the Australian environment. Accounts from Canada report that within a relatively short period of time during the 2007 June-July spawning period for common carp, the mortality of carp may have exceeded 24,000 fish across nine affected lakes in south-central Ontario [17]. It is estimated that 90,000 tonnes of carp were disposed of at local landfills, equating to between 13,000 and 24,000 fish. These estimates did not include the carp that were disposed of on private land or those that decomposed in the lake. It was noted that while the fish died during this period of time, it was not known how long the fish had been infected. It was also noted that concurrent disease might have lowered the amount of virus needed to kill the fish, or that other concurrent bacterial infections might have been the primary cause of death after being debilitated by CyHV-3, indicating a synergistic action between the pathogens.

The events in Canada in 2007 and again in 2008 shared two important common features with other KHV-Associated wild carp mortality events. Firstly, CyHV-3 outbreaks in wild carp populations are temperature dependent with the range being 18-26° C. Secondly, only common carp have been affected, a finding supported by the research of McColl [1] who, having conducted infectivity tests with a variety of non-target fish species, concluded that that spill-over infections and species jump are highly unlikely with CyHV-3. found that. It is important to note that the presence of the virus in the waterways does not always lead to mass mortality events, with the critical predisposing factors being unclear [17]. However, the synergistic effects of other pathogens exacerbating the impact of the virus are a recognised factor in terms of magnitude of the die-off event.

In Japan, where koi are an important ornamental commodity and common carp are extensively farmed, the invasion by CyHV-3 of freshwater systems has caused large mass mortality events in wild carp populations. From April to July of 2004, it is estimated that more than 100,000 fish died in Lake Biwa, representing potentially 70% of the fish in the lake [28]. No further mass mortality events have been recorded from Lake Biwa, with the fish that survived the initial infection having developed antibodies and enhanced resistance to the virus [41].

Limitations

The major limitation of this project is that while the systematic review process was followed faithfully, little primary research existed on the topic to make conducting the review worthwhile and fruitful. This has been previously identified as an issue for systematic reviews [42]. In the situation of this project, while it was thought during the project proposal phase that there would be literature – either published articles or media – on the potential impacts of the carp herpesvirus to the environment, ecology or to human sensibilities, there in fact was very little. This was surprising given the world-wide reach of the virus and the fact that the virus is also present in countries where carp are native and have value as a cash crop. We can only report that there is a lack of high-quality evidence to support concerns about the potential for impact on humans of the carp herpesvirus and hence little direct relevance to human health.

Conclusion

The key findings of this series of literature searches include:

1. There is no published evidence of a risk that the virus has zoonotic potential.
2. Even in countries where carp are valued, there is little published on how humans react emotively to mass mortality events of carp or other fish. The reported human reactions were with regard to income loss for fisherman when fish had commercial value.
3. It could be reasonably expected that in certain locations – such as lakes and rivers that intersect urban environments – there is likely to be a public reaction to mass mortality events of carp. Rapid clean-up of the dead fish will mitigate adverse reactions from the public and in the media.
4. The virus does not have a 100% kill rate in naturally-occurring mass mortality events of carp, and those fish that survive the initial infection have immunity.
5. Higher kill rates are associated with carp spawning season and co-infections by other pathogens.

Recommendations

While there was little in the published literature on the impact on human health of a mass die-off of carp should the virus be released into Australian inland waterways, it could be reasonably assumed that the public, particularly children, may react with distress to large numbers of dead and dying fish in visible or recreational waterways. It is recommended that any plans for release of the virus also include strategies for management of collection and disposal of the dead fish, together with a communication plan for the general public.

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Appendix 1

This appendix provides further information on the databases used in the literature searches and systematic review processes.

Systematic review

The aim of a systematic review is to develop a concise summary of the best available evidence that addresses a clearly defined question in a particular area of interest [43]. A systematic review uses explicit and rigorous methods to identify, critically appraise and synthesise relevant research around a specific research question. As the process is criterion-based and follows a series of standardised and transparent steps, the review process can be replicated by another researcher working separately and independently. A systematic review is undertaken by a team of at least two persons, or more as needed depending upon the scope of the research question and the anticipated volume of research articles that may be uncovered. The outcome of the process is collective and reduces potential bias, therefore adding rigour to the research findings.

SuperSearch (Proquest)

SuperSearch is a name given by the ANU Library to the Summon® Service from the vendor Proquest. Searching SuperSearch provides results from Scopus, MedLine (Medline from Ovid), Web of Science, amongst others from the databases that ANU Library subscribes to and therefore has fulltext access. It is a web-scale discovery tool that searches the contents of multiple library catalogues and databases simultaneously. "Web-scale" refers to the attempt to match the kind of broad and deep search familiar to Google and other web search tools. SuperSearch uses an index of keywords to formulate search results from the ANU subscription content in the first instance. The Summon Index contains over 2 billion items. Content is indexed at the record level (full-text, metadata, or both) from information provided directly by publishers and content providers.

However, SuperSearch does not offer the more sophisticated search options that may be found when accessing the native interface for the individual databases and therefore some results may be missed. To overcome this, supplemental searching of the databases directly is recommended.

Scopus

Scopus is the largest abstract and citation database of peer-reviewed research literature with more than 20,500 titles from more than 5,000 international publishers. It includes all MEDLINE content as well as 30million+ more records. The scope is beyond just biomedical content and includes some conference papers.

Scopus enables the capacity to limit or exclude the displayed search results to specified keywords selected in the limits of the search, as well as the capacity to sort by cited references.

Proquest

ProQuest contains cross disciplinary and allied health content, including Sociological Abstracts which indexes and provides abstracts for international literature in sociology and related disciplines in the social and behavioural sciences. Included are journal articles, books, book chapters, dissertations, and conference papers, as well as citations to book reviews from 1952 to the present. ProQuest also contains newspaper content.

PubMed

PubMed comprises more than 23 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.

PubMed searches that are limited to MeSH controlled vocabulary or the MEDLINE subset will only produce MEDLINE citations in the results. Using a broader keyword search results in a more extensive although less controlled set of literature.

Factiva

Factiva is a global news database of nearly 33,000 premium sources, including licensed publications and influential websites. News and business information is provided in 22 languages from 118 countries. Source documents include newspapers, magazines, newswires, media programs, websites, company reports and images from Reuters and Knight Ridder.