



Cardiomyopathy Syndrome (CMS) in Atlantic salmon

WP4. Literature review



WP 4. Deliverables

- ▶ Report in Norwegian
- ▶ Fact sheet in Norwegian
- ▶ Scientific review
- ▶ PP- presentation

An Epidemiological study of CMS: Transmission, risk factors and disease development in Norwegian salmon farming

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REVIEW

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Cardiomyopathy syndrome in Atlantic salmon *Salmo salar* L.: A review of the current state of knowledge

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Abstract

Cardiomyopathy syndrome (CMS) is a severe cardiac disease affecting Atlantic salmon *Salmo salar* L. The disease was first recognized in farmed Atlantic salmon in Norway in 1985 and subsequently in farmed salmon in the Faroe Islands, Scotland and Ireland. CMS has also been described in wild Atlantic salmon in Norway. The demonstration of CMS as a transmissible disease in 2009, and the subsequent detection and initial characterization of piscine myocarditis virus (PMCV) in 2010 and 2011 were significant discoveries that gave new impetus to the CMS research. In Norway, CMS usually causes mortality in large salmon in on-growing and brood-fish farms, resulting in reduced fish welfare, significant management-related challenges and substantial economic losses. The disease thus has a significant impact on the Atlantic salmon farming industry. There is a need to gain further basic knowledge about the virus, the disease and its epidemiology, but also applied knowledge from the industry to enable the generation and implementation of effective prevention and control measures. This review summarizes the currently available, scientific information on CMS and PMCV with special focus on epidemiology and factors influencing the development of CMS.

KEYWORDS

Atlantic salmon (*Salmo salar* L.), cardiomyopathy syndrome, piscine myocarditis virus, PMCV, CMS

1 | INTRODUCTION

The establishment of large-scale intensive farming of Atlantic salmon *Salmo salar* L. facilitated a dramatic change in conditions for pathogen transmission and growth. This has led to emergence and widespread distribution of several infectious diseases within the industry (Rimstad, 2011).

Cardiomyopathy syndrome (CMS), a severe cardiac disease of Atlantic salmon, made its entry in Norwegian salmon farming in the mid-1980s (Amin & Trasti, 1988) and was subsequently detected in the Faroe Islands (Poppe & Sande, 1994; Poppe & Seierstad, 2003), Scotland (Rodger & Turnbull, 2000) and Ireland (Rodger, McCleary, &

Ruane, 2014). A disease resembling CMS has also been detected in Canada (Brookelbank & Raverty, 2002). Due to the late onset of disease during the production cycle and a large number of outbreaks, CMS has significant economic impact at both company and industry levels in Norway (Brun, Poppe, Skrudland, & Jarp, 2003). In 2009, it was demonstrated that CMS is a transmissible disease (Bruno & Noguera, 2009; Fritsvold et al., 2009), and subsequently in 2010 and 2011, two separate research groups linked CMS to a virus resembling viruses of the *Totiviridae* family (Haugland et al., 2011; Lovoll et al., 2010). The discovery of piscine myocarditis virus (PMCV) had a significant impact on the development of new diagnostic, research and monitoring tools and has consequently increased our knowledge about the

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Kardiomyopatisyndrom

Sykdommer kardiomyopatisyndrom (CMS) har lenge vært ukjent, men det ble tidlig mistenkt at piscint myokarditt virus (PMCV) ble beskrevet sammenheng mellom tilstedeværelse og mengde relaterte patologiske endringene i hjerte. CMS tyndepunkt. Det registreres i overkant av 100 høyere siden sykdommen ikke er meldepiktig. I Færøyene, CMS-lignende patologi er også beskrevet betydelige økonomiske tap for næringen.

Kardiomyopatisyndrom (CMS)

CMS er en kronisk sykdom i hjertet hos atlantisk laks. Sykdommen opptrer oftest hos fisk med vekst og i normalt hold. Dødeligheten utvikler seg langsomt, men med episoder av forhastet dødelighet i forbindelse med stress, håndtering, ugunstige miljøforhold eller gen- sykdomsstress. Diagnosen CMS stilles på grunn av kliniske symptomer, funn ved obduksjon, histopatologisk undersøkelse. Obduksjonsfunn er sirkulasjonsforstyrrelser og blødning i hjertesekken. Histopatologiske funn er betennelse og nekrose i hjertemuskelceller og i hjertets svampaktige muskellag (spongios myokard). Skadene opptrer først i forkammeret, før de seg videre til hjertekammeret.

Piscint myokarditt virus (PMCV)

PMCV er et relativt lite og enkelt oppbygg med et kappeprotein som omslutter arvestoffet. Det viktigste målorgan for infeksjon er laksens hjertemuskelceller. Det er detektert både virusets arvestoff og kappeprotein i infisert vev og celler. Viruset hovedsakelig i CMS-syk laks i oppdrett, genetiske forskjellene mellom virusisolater

Reservoar for PMCV

Laks i oppdrett er det viktigste kjente reservoaret for PMCV. I tillegg er viruset påvist hos andel villaks og hos vassild. PMCV fra villaks er ulikt virus fra vill og oppdrettet laks (forskjell på nukleotide nivå). I 2017 ble det rapportert funn av PMCV og CMS relatert til rensefisk i Irland.

Kardiomyopatisyndrom

Sykdomsutvikling - Ager



Overview of review



- ▶ CMS - Cardiomyopathy syndrome
- ▶ PMCV - piscine myocarditis virus
- ▶ Epidemiology
 - ▶ Occurrence
 - ▶ Reservoirs
 - ▶ Transmission
 - ▶ Risk factors
- ▶ Prevention and control
- ▶ Economy
- ▶ Knowledge gaps



CMS - cardiomyopathy syndrome



- ▶ Severe cardiac disease affecting Atlantic salmon
- ▶ Occurrence
 - ▶ Norway
 - ▶ Faroe Islands
 - ▶ Scotland
 - ▶ Ireland



CMS - cardiomyopathy syndrome



- ▶ Onset and course of disease:
 - ▶ Typically second year of sea phase, but also earlier
 - ▶ Acute: Sudden high mortality
 - ▶ Chronic: Prolonged period of moderate mortality



Photo: Trygve Poppe

CMS – clinical signs



- ▶ None or signs of lethargy
- ▶ Signs of circulatory failure
 - ▶ Protruding eyes (Exophthalmia)
 - ▶ Ventral skin bleedings
 - ▶ Raised scales
- ▶ Internal findings
 - ▶ Ascites
 - ▶ Blood clots in the pericardial cavity.
 - ▶ Enlarged or ruptured atrium and/or sinus venosus = «Hjertesprekk»
 - ▶ Discoloured liver with fibrinous casts



Photo: Per Anton Sæther,
MarinHelse AS

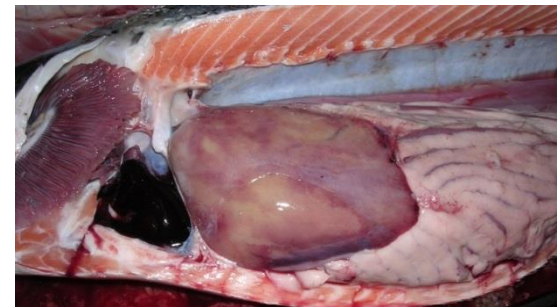


Photo: Brit Tørud,
Norwegian Veterinary Institute

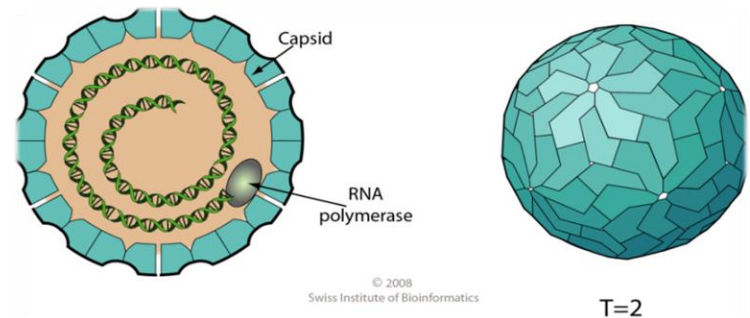
PMCV – piscine myocarditis virus



- ▶ Similarities with *Totiviridae* family
 - ▶ A family that infects protozoan parasites and fungi
 - ▶ Transmission during cell division, sporogenesis or cell fusion
- ▶ Recently several more complex “toti-like” viruses

- ▶ Structure PMCV:
 - ▶ First toti-like virus found vertebrate host
 - ▶ Spherical ~50nm
 - ▶ Non-segmented ds RNA-genome
 - ▶ Non-enveloped (naked) → resistant (?)

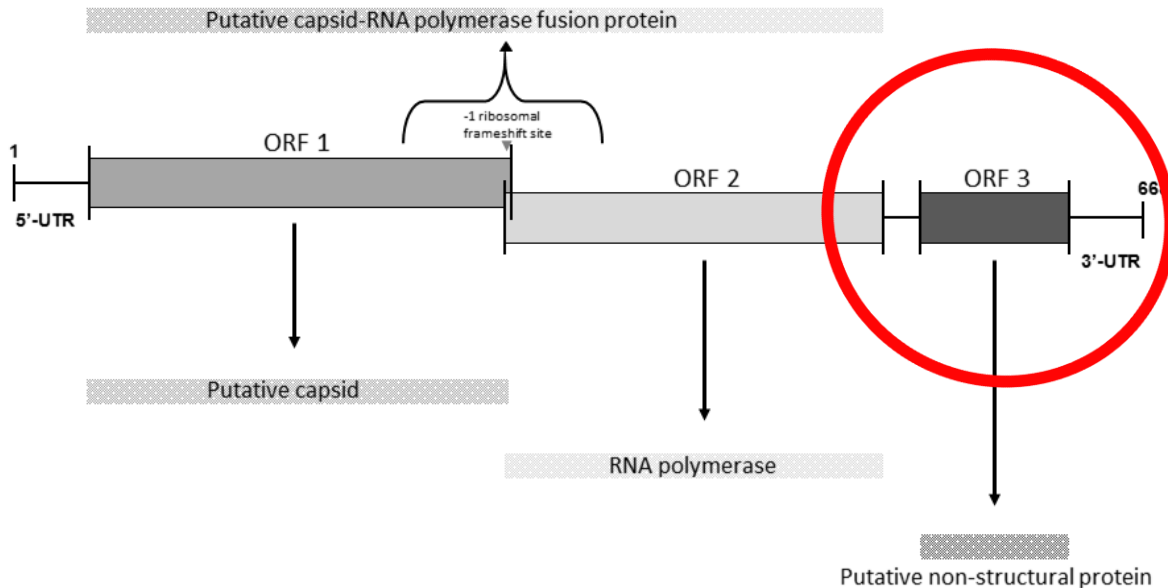
- ▶ Biophysical properties:
 - ▶ Unknown



Totiviridae

Swiss Institute of Bioinformatics (SIB) used with permission

PMCV – genome



*Illustration: Aase B. Mikaelson
NMBU*

- ▶ 6.688bp
- ▶ Three open reading frames (ORF1, ORF2 and ORF3)
- ▶ ORF3: Exclusive for viruses infecting vertebrate hosts
 - ▶ Research is focused on the ORF3

PMCV – genetic variation



- ▶ Homogenous population in Norway (one genogroup)
- ▶ Most divergent: 98.6% nucleotide identity
- ▶ Atlantic argentine 86% nucleotide identity
- ▶ Virulence factors:
 - ▶ Three positions on the ORF3 have been suggested

Illustration: Åse Helen Garseth, NVI



CMS & PMCV – diagnostic tools



- ▶ The CMS diagnosis is based on:
 - ▶ Clinical observations and autopsy
 - ▶ Histopathology
 - ▶ Differential diagnosis: PD and HSMI
- ▶ PMCV specific real-time PCR:
 - ▶ High correlation between virus load and pathological changes
 - ▶ Widely used for screening
 - ▶ Patent by Pharmaq Analytiq

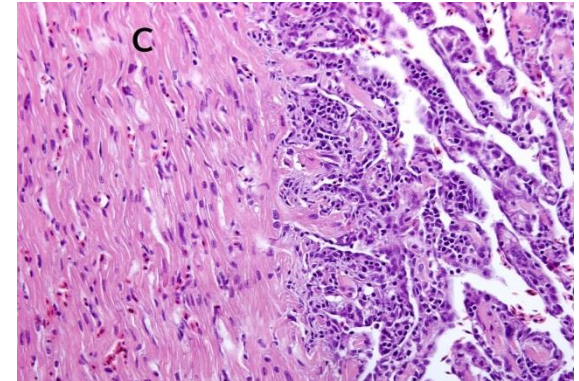


Photo: Trygve Poppe

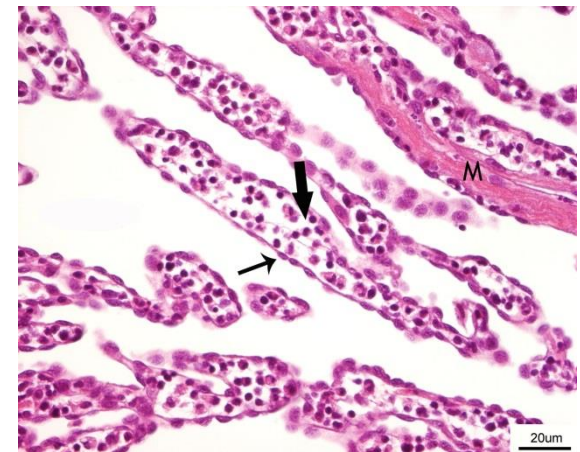


Photo: Camilla Fritsvold,
Norwegian Veterinary Institute

CMS & PMCV – diagnostic tools



▶ In situ hybridization:

- ▶ Detects virus specific nucleic acids in fish tissue with histopathological changes
- ▶ Not used for routine diagnostics

▶ ImmunHistoChemistry (IHC):

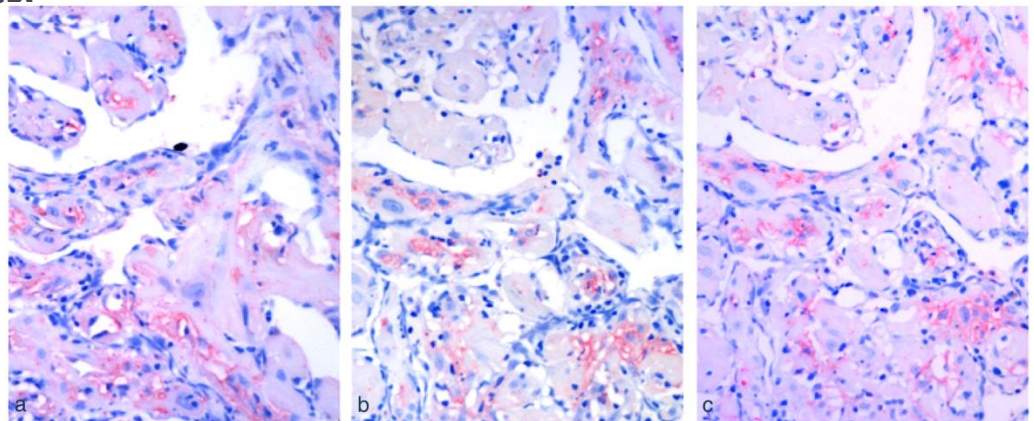
- ▶ Detects PMCV specific proteins
- ▶ Not available for routine use due to lack of antibodies

▶ Cell culture:

- ▶ PMCV replicates in fish cell lines.

but at too low levels,
and too weak CPE.

Immunohistochemistry detects PMCV specific proteins by the use of labelled antibodies
Photo: Gulla *et al.* 2012



CMS & PMCV - epidemiology



▶ Reservoir PMCV:

- ▶ Farmed Atlantic salmon
- ▶ Farmed escapees
- ▶ Found in a few wild salmon*
- ▶ PMCV found in cleaner fish in Ireland
- ▶ Not found in environmental samples, but in mucus, faeces and salmon lice in infected cage

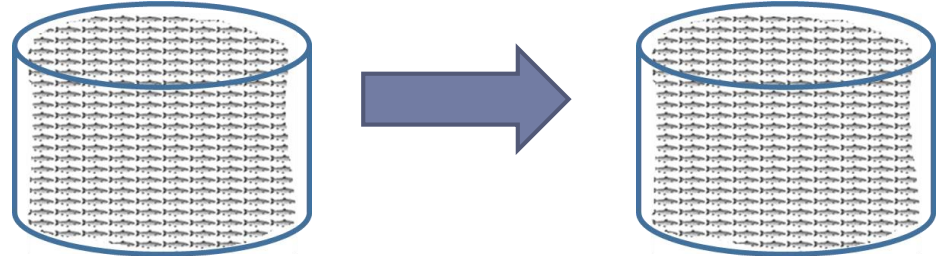


A virus sharing 86 % nucleotide identity with PMCV has been found in Atlantic Argentine
Photo: Wikipedia

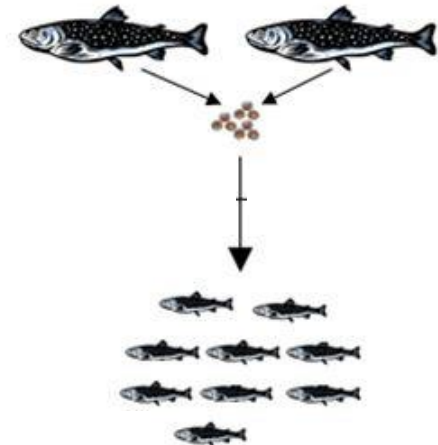
Transmission routes:



► Horizontal transmission



► Vertical transmission is under investigation



Risk factors



- ▶ Time in sea
- ▶ Size of population
- ▶ Infection pressure
 - ▶ CMS in neighbouring farms and distance
- ▶ CMS in previous cohorts
- ▶ HSMI in same cohort

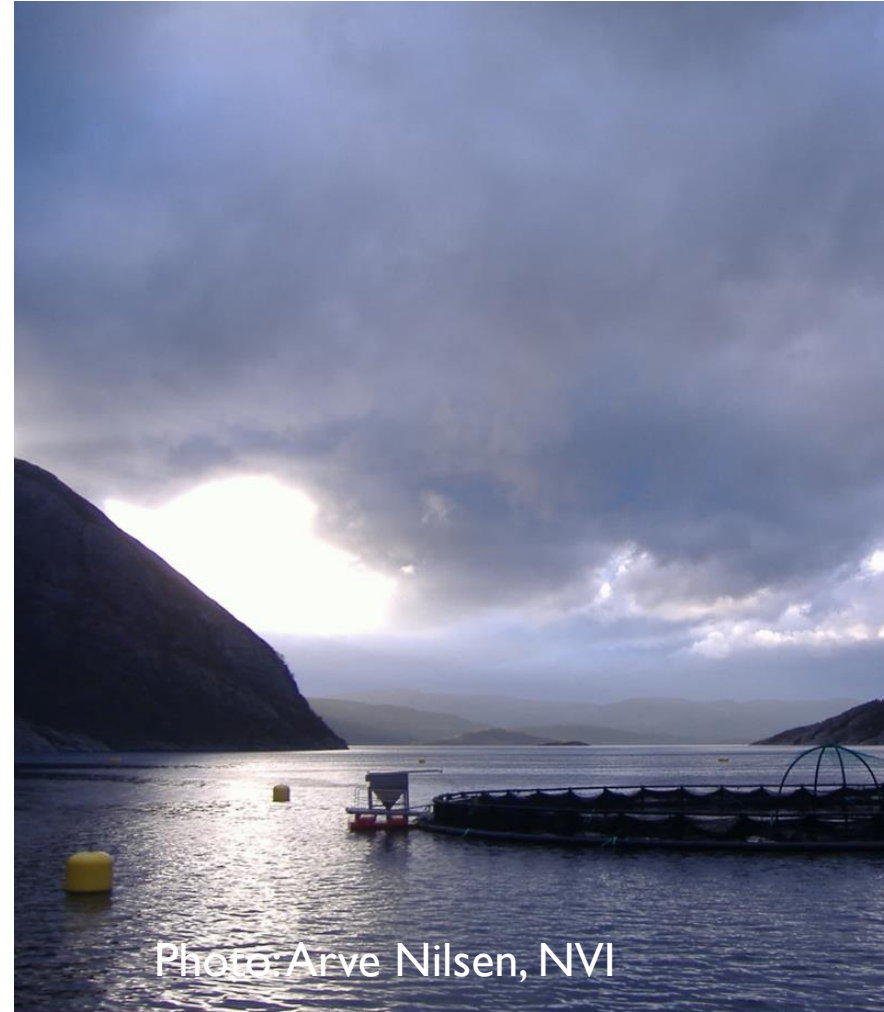


Photo: Arve Nilsen, NVI

CMS - prevention and control



▶ Biosecurity

- ▶ Pathogen free stock
- ▶ All-in all-out, fallowing
- ▶ Infection pressure from neighbours
- ▶ Time at sea
- ▶ Cleaning and disinfection (robust)

▶ Screening for PMCV (or CMS)

- ▶ Early detection
- ▶ Before the fish is moved



Husbandry and Animal welfare



- ▶ Affected fish are fragile
- ▶ General advice:
 - ▶ Know your fish!
 - ▶ Avoid stress!
 - ▶ Early slaughter
 - ▶ On-site harvesting



- ▶ Delousing - mechanical methods - mortality
crowding-pumping-flushing-brushing-elevated temperatures

Modulating host response



▶ Vaccination

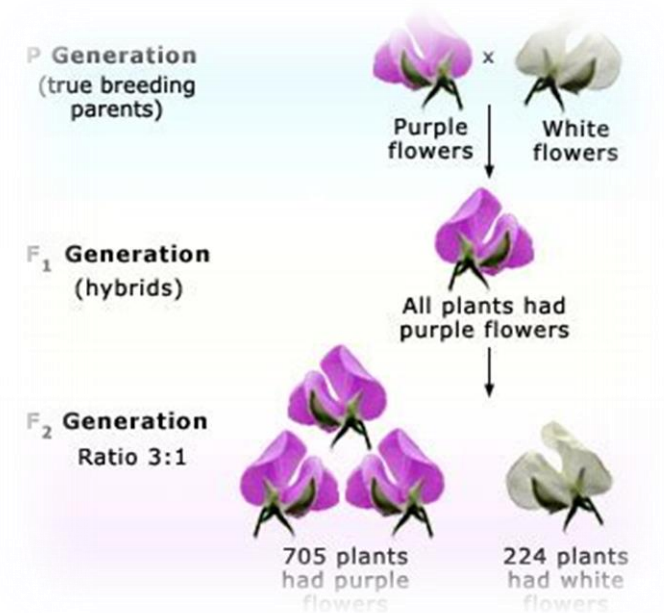
- ▶ Pharmaq is working on a vaccine
- ▶ Lack of a cell line

▶ Selective breeding

- ▶ Cardiovascular capacity
- ▶ High heritability for resistance
- ▶ QTL-selected eggs are available

▶ Feed

- ▶ Lower lipid content and higher Ω -3/ Ω -6 ratio (PUFAs)
- ▶ Effect demonstrated in trials



Legislative control



- ▶ Not a notifiable disease

- ▶ The challenge:
 - ▶ CMS 1985
 - Limited occurrence
 - Unknown cause
 - ▶ Transmissible disease 2009
 - ▶ PMCV 2010
 - Disease and virus ubiquitous



CMS - economic impact



- ▶ > 100 cases per year
- ▶ 2000:
 - ▶ ~4.5-8.8 million €
- ▶ 2007:
 - ▶ ~25 million €

Not including costs for
prevention and extra labour



Photo: Per Anton Sæther, MarinHelse

Knowledge gaps



▶ PMCV:

- ▶ Characterize proteins that are coded for by the virus RNA
- ▶ Understand mechanisms for infection and replication in the host
- ▶ Develop cell culture

▶ CMS:

- ▶ Pathogenesis
- ▶ Factors that trigger disease development in infected fish
- ▶ Can infected fish get rid of virus?

▶ Transmission, prevention and control

- ▶ Can PMCV be transmitted vertically?
- ▶ Virus reservoir (beyond the farmed salmon)
- ▶ The importance of smolt from freshwater phase?

Read more about CMS and the project

<http://www.fhf.no/prosjektdetaljer/?projectNumber=901118>

<https://www.vetinst.no/rapporter-og-publikasjoner/rapporter/2017/kardiomyopatisyndrom-cms-hos-laks>

<http://onlinelibrary.wiley.com/doi/10.1111/jfd.12735/epdf>



1 | INTRODUCTION

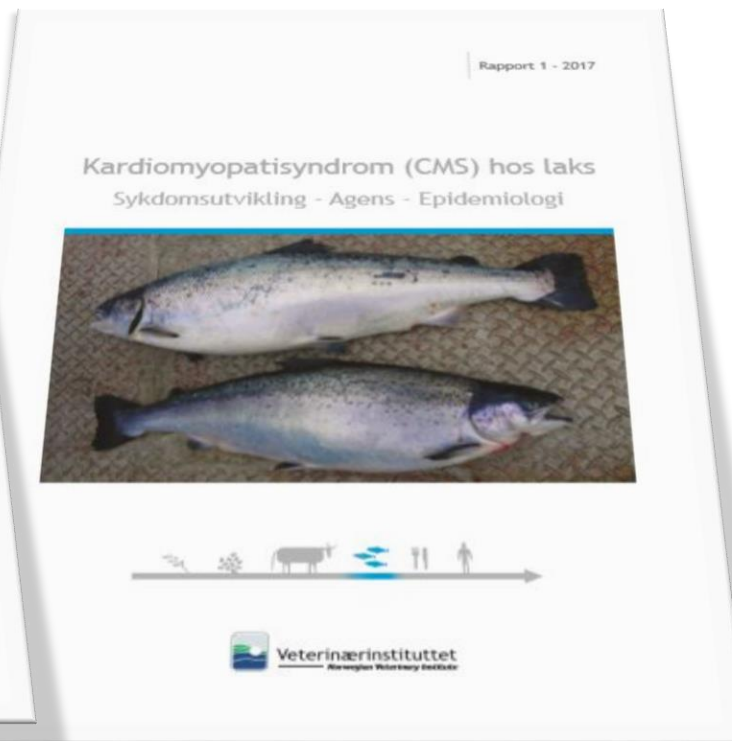
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