Epizootics in harbour seals *(Phoca vitulina)*: clinical aspects

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ABSTRACT

Epizootic diseases causing considerable mortality in harbour seal populations have mainly been reported from the waters of the United States and Europe. Such die-offs were largely attributable to viral infections. Several hundred individuals died from respiratory infections caused by Influenza A viruses at the coast of New England, USA, in 1979, 1980 and 1982. More than 53,000 harbour seals were killed in European waters by Phocine Distemper Virus (PDV), a morbillivirus, in two outbreaks in 1988 and 2002. For several other epizootics of smaller scale in the waters of the Atlantic and Pacific coast of the USA and, most recently, in Danish and Swedish waters in 2007 the causes remain unclear, although characteristic respiratory symptoms and interstitial pneumonia suspicious of viral etiology were detected as well as occasionally bacterial infections caused by *Erysipelothrix rhusiopathiae* and *Pseudomonas aeruginosa*. Mass mortalities caused by biotoxins, direct human interactions or changes in oceanographic conditions have so far not been described for harbour seals. However, high organochlorine loads detected in European harbour seal populations and suspected to impede immune functions, were considered an aggravating factor in the 1988 morbillivirus epizootic. Establishing supranational stranding networks is a key prerequisite for the detection of future unusual die-offs in marine mammals. Detailed post-mortem investigations of all organ systems are essential for targeted etiological studies towards the causes of mass mortalities in seals.

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INTRODUCTION

Mass mortalities in harbour seals *(Phoca vitulina)* have exclusively been reported in the United States and European waters (Table 1). The seeming concentration of such die-offs on the northern Atlantic coast may be a consequence of supranational stranding networks operating in these areas and having capabilities to detect and diagnose seal mortality. Infectious diseases were determined to be the cause in some of the die-offs while in some cases no cause could be elucidated. The number of animals killed varied widely among the different outbreaks (Table 1). In this chapter, clinical aspects and epidemiology of different epizootics are reviewed.

VIRAL DISEASES

Phocine distemper die-offs in 1988 and 2002 in European waters

In 1988 and 2002 two large-scale epizootics occurred among harbour seals in European waters. Both epizootics started at the small Danish island of Anholt located in the Kattegat linking the Baltic and the North Seas. These outbreaks resulted in the deaths of more than 23,000 harbour seals in 1988 and 30,000 in 2002. In both years the cause of mortality was identified as Phocine Distemper Virus (PDV) (Kennedy 1990, Jensen *et al.* 2002, Müller *et al.* 2004). Details on the different geographical and chronological patterns of dispersal as well as population aspects are described elsewhere (Härkönen *et al.* 2006, Seibel *et al.* 2007, Härkönen and Isakson 2010).

Table 1. Mass mortalities affecting harbour seal populations.

Year	Geographic location	Reported number dead animals	Etiology
1978-80 1982	Cape Cod, Massachusetts, U.S.	400	Influenza A virus
1988	European waters	23,000	Phocine Distemper virus
1991	New Jersey, U.S.	34	Unknown *Erysipelothrix rhusiopathiae* and *orthopoxvirus* present
1992	Oregon, Washington, U.S.	29	Unknown
1992	Maine, Massachusetts U.S.	24	Unknown, *Morbillivirus* and/or Influenza virus suspected
1997	California, U.S.	90	Unknown, *Pseudomonas aeruginosa* associated with pneumonia virus suspected
1998	Belgian and French North Sea	11	*Morbillivirus*
2000	California, U.S.	26	Unknown, viral pneumonia suspected
2002	European waters	30,000	Phocine distemper virus
2003-2004	Gulf of Maine, U.S.	Unknown	Unknown
2007	Danish and Swedish waters of the Kattegat and Skagerrak	285	Unknown

The virus family *Paramyxoviridae* comprises 2 subfamilies, *Paramyxovirinae* with the 3 genera *Respirovirus*, *Rubulavirus* and *Morbillivirus*, and *Pneumovirinae* with the genera *Pneumovirus* and *Metapneumovirus* as well as unclassified paramyxoviruses. They include some of the most important pathogens of humans and animals. The morphologically distinguishing features for viruses of the subfamily *Paramyxovirinae* are the size and shape of the nucleocapsids (diameter of 18 nm, 1 μm in length, a pitch of 5.5 nm). They have a left-handed helical symmetry. The biological criteria are: (a) antigenic cross-reactivity between members of a genus and (b) the presence *(Respirovirus* and *Rubulavirus)* or absence *(Morbillivirus)* of neuraminidase activity (www.ncbi.nlm.nih.gov/-ICTVdb/Ictv/index.htm).

Morbillivirus infections can cause significant mortalities in humans and animals (Barrett 1999, Baumgärtner *et al.* 2003). Measles virus is responsible for up to two million childhood deaths in humans annually in the developing world, while *Pestes des petits ruminants* viruses cause severe epizootics in domestic and wild ruminants in areas of the world where it remains endemic (Barrett 1999). Rinderpest virus causing a highly contagious disease associated with massive mortality in domestic and wild ruminants has been eradicated globally due to successful vaccination campaigns in the last decade. Canine Distemper Virus (CDV) causes a fatal disease in many species of carnivores. New morbilliviruses with potentially important ecological consequences for marine mammals have been discovered over the past 15 years: Phocine Distemper Virus (PDV) in seals, cetacean morbilliviruses (CMV), including porpoise morbillivirus (PMV), and dolphin morbillivirus (DMV) detected in dolphins, whales and porpoises (Kennedy 1998, Wohlsein *et al.* 2007b). PDV and CDV are most closely related among the morbilliviruses. Arctic seals may have been infected by CDV several hundreds or thousands of years ago from terrestrial carnivores such as wolves, foxes, dogs or polar bears, after which the virus may have evolved into PDV (Barrett 1999). PMV and DMV constitute a separate branch in the phylogenetic tree, more distant from the presumed ancestral progenitor virus (Rima *et al.* 1992, Blixenkrone-Møller *et al.* 1994, Barrett *et al.* 1995, Müller *et al* 2000, Wohlsein *et al.* 2007a). Samples taken from affected harbour and harp seals in Ireland, Denmark and the Netherlands in 1988 indicated that PDV was genetically identical indistrict geographical regions. Samples obtained from harp seals from Ireland, Denmark and the Netherlands during the 1988 PDV epizootic indicated that the virus was genetically identical in these regions (Visser *et al.* 1990, Barrett *et al.* 1992). A comparison of the PDVs causing the 2002 and 1988 outbreaks showed that both strains were at 97% identical in the P gene sequence (Jensen *et al.* 2002, Müller *et al.* 2004).

Clinical manifestations of PDV in harbour seals include fever, occulonasal discharge, conjunctivitis, ophthalmia, keratitis, coughing, dyspnoea, diarrhoea, abortion, increased buoyancy due to the emphysema and the inability to dive (Kennedy *et al.* 1989, Bergman *et al.* 1990, Kennedy 1998). The incubation time of experimental PDV morbillivirus infection in harbour seals is at least 5 to 12 days (Harder *et al.* 1990). In dogs, depending on the immune status of the animals, the virus CDV can cause an abortive, subclinical or severe systemic, often lethal infection (Krakowka *et al.* 1985). The virus is shed in all excretions from infected animals and is transmitted through direct contact and inhalation. Systemic spread is achieved through infected macrophages and lymphocytes transporting the virus to permissive epithelial, mesenchymal and neuroectodermal tissues (Caswell and Williams 2007). The predominant pathological finding in PDV-infected seals is an interstitial and purulent pneumonia with marked pulmonary alveolar and interstitial emphysema (Kennedy *et al.* 1989, Bergman *et al.* 1990, Kennedy 1998, Jauniaux *et al.* 2001). *Bordetella bronchiseptica* is the most common bacterium isolated from animals with secondary bacterial infections (Baker and Ross 1992, Jensen *et al.* 2002, Müller *et al.* 2002) but less common bacteria including *Mycoplasma* spp. were also found (Kennedy 1998). Common patho-histological findings are lymphocytic depletion in lymphoid tissues and a non-suppurative encephalitis (Kennedy *et al.* 1989, Bergman *et al.* 1990, Kennedy 1998, Jauniaux *et al.* 2001). Cytoplasmic and intranuclear viral inclusion bodies are present in various organs

including lung, liver, kidneys, pancreas, intestine and brain (Kennedy *et al.*1989, Bergman *et al.* 1990, Kennedy 1998). Experimentally neutralising serum antibodies were apparent in seals 16 days post infection (Harder *et al.*1990).

A main hypothesis for the source of the 1988 epizootic is that arctic harp seals *(Phoca groenlandica)* acted as both a reservoir and the primary vector for PDV (Dietz *et al.* 1989, Henderson *et al.*1992, Markussen and Have 1992). Harp seals were not documented around the Anholt Island in Denmark, the site where both epizootics in the North Sea started but were seen in the vicinity of harbour seal haulout sites in the North Sea (Heide-Jørgensen and Härkönen 1992). In addition, unusual presence of harp seals was reported in 1987 on the European coasts around the North Sea and adjacent waters, and they may have transferred the disease to harbour seals (Goodhart 1988, McGoutry 1988). Over the years following the 1988 epizootic, there were no signs that PDV had continued to circulate among European harbour seals (Jensen *et al.* 2002, Thompson *et al.* 2002, Müller *et al.* 2004, Siebert *et al.* 2007), except for some cases in 1998 on the Belgian and northern French coast (Jauniaux *et al.* 2001), and the new outbreak in 2002 was most likely the result of another introduction of the virus from an unknown source. As the disease again started at Anholt Island, this haulout site requires closer scrutiny. Its most striking feature is that harbour seals haul out in large numbers (500-1000) on a limited area of sandy beaches on the eastern end of the island. This locality is shared with grey seals *(Halichoerus grypus)*, which only occur in low numbers (5-10 animals). Harbour and grey seals haul out very close together, and are not separated in groups as seen in most other localities where the grey seal numbers are larger. Consequently, the grey seals at Anholt are potential candidates for transferring PDV to harbour seals. Grey seals in general have larger activity ranges than harbour seals. It is still puzzling why the epizootic started at Anholt and not *e.g.* in the western Dutch Wadden Sea, where more than 1,100 grey seals are present and over 150 pups are born annually (Reijnders *et al.* 1995). Mixed colonies of grey and harbour seals are also common here.

Environmental factors must be considered for their possible influence on variation in mortality during the PDV-epizootics. The role of organochlorine (OC) contamination, through impeding immune system function, was considered a predisposing factor in the 1988 epizootic, although a causal relation could not be firmly established (Hall *et al.* 1992, Reijnders and Aguilar 2002). Novel compounds of concern, such as organotins and brominated flame retardants (*e.g.* polybrominated diphenyl ethers), may pose a new threat to the immune fitness of seals. However, data on tissue concentrations of these compounds in seals in the North Sea area are scarce (Boon *et al.* 2002, Hall *et al.* 2003, Law *et al.* 2003). Moreover, information on the immuno-toxicological impact of these compounds on marine mammals is currently lacking. Therefore, no conclusions about the role of these compounds in the resistance of seals to PDV or other infectious diseases can be drawn at this time. Finally, another factor of predisposition is associated with the host species, since harbour seals within European waters are highly susceptible while other species, such as harp and grey seals, are more resilient (Harkönen *et al.* 2006). *Morbillivirus* seropositive harp seals have been reported in 1985 without associated disease (Dietz *et al.* 1989), while all tested harbour seals were negative before the first epizootics (naïve population). This confirmed that harp seals could be considered a vector of the virus to the naïve harbour seal population, predisposing it for the severe 1988 epizootics (Stuen *et al.* 1994).

Influenza A,
Cape Cod 1979-80, 1982

From 1979 to 1980 and again in 1982, more than 450 harbour seals were found dead on the coast of Cape Cod, Massachusetts, US. Investigations revealed that Influenza A virus was responsible for the disease (Geraci *et al.* 1982, Hinshaw *et al.* 1984).

Influenza viruses belong to the family *Orthomyxoviridae*. These viruses are pleomorphic, enveloped and have a size of 80 to 120 nm in diameter. The nucleocapsids have helical symmetry. The genome of influenza A viruses consists of 8 segments of single-

stranded RNA of negative polarity coding for at least 11 proteins (www.ncbi.nlm.-nih.gov/ICTVdb/ Ictv/index.htm). Influenza A viruses have an extraordinary broad host spectrum and have been isolated from birds (where they have their natural reservoir), to horses, pigs, cats, dogs, humans and marine mammals (Vahlenkamp and Harder 2006).

Influenza A viruses have also been isolated from harbour seals. An influenza A virus of subtype H7N7 (A/Seal/Mass/1/80), was present in harbour seals dying at the New England Coast in 1980 (Geraci *et al.* 1982). *Mycoplasma* spp. were isolated concurrently from these animals. Another influenza A virus, subtype H4N5 (A/Seal/Mass/133/82), was obtained from harbour seals from neighbouring locations between June 1982 and March 1983 (Hinshaw *et al.* 1984). In winter 1991-1992 two additional isolates of subtypes H4N6 and H3N3 (A/Seals/MA/3807/91, A/Seal/MA/ 3810/91, A/Seal/MA/3911/92) were obtained from these populations (Callan *et al.* 1995). All influenza A viruses that were isolated from seals were antigenically and genetically most closely related to avian influenza viruses, suggesting frequent spill-overs from pelagic birds (Kennedy-Stoskopf 2001). No evidence for stable circulating seal-adapted lineages of influenza A viruses have been obtained so far. The incubation period of the influenza virus infections in naturally infected seals seems to be 3 days or less (Webster *et al.* 1981, Geraci *et al.* 1984, Hinshaw *et al.* 1984). According to experimental inoculation trials, all isolates from harbour seals were able to replicate in ferrets, cats, pigs and phocid seals, including harbour, ringed and harp seals. (Webster *et al.* 1981, Geraci *et al.* 1984, Hinshaw *et al.* 1984).

Clinical signs of natural influenza infection were similar to those described in seals with PDV. These included dyspnoea, lethargy, blood-stained nasal discharge and subcutaneous emphysema. Pulmonary lesions were predominantly characterised by necrotising bronchitis and bronchiolitis, and hemorrhagic alveolitis (Geraci *et al.* 1982, Hinshaw *et al.* 1984).
So far, Influenza A virus infections associated with mortality in harbour seals have been found exclusively on the east coast of the United States. However, Influenza B virus (B/Seal/Netherlands/1/99), previously thought to be exclusively a human pathogen, was isolated from the respiratory tract of a single juvenile harbour seal from the Dutch Wadden Sea with clinical signs, which recovered from the infection (Osterhaus *et al.* 2000).

UNKNOWN CAUSES OF MORTALITIES

Mass mortality in Danish and Swedish waters of the Kattegat and Skagerrak in 2007

The most recent outbreak of disease leading to increased mortality of harbour seals in Europe began in 2007, again on the small Danish island of Anholt on 15 June 2007 (Härkönen *et al.* 2008). Clinical signs of diseased seals and gross pathological findings were similar to those observed in 1988 and 2002. It was initially believed that PDV was the cause of the third die-off.

From Anholt the disease spread to other major harbour seal colonies in the Kattegat and Skagerrak over the next months, and single carcasses where found until the end of 2007. In the Danish part of the Kattegat a total of 163 dead seals were found washed ashore. The majority of these animals were pups born in the same year (149 individuals, standard length (length from nose to tail when the seal is lying with its belly up <100 cm Härkönen *et al.* 2008), 10 were subadults (standard length 101-139 cm), and 4 were adults (standard length >140 cm). The first diseased seals in Swedish colonies were observed on 9 July. By 22 September 2007, a total of 122 carcasses had been collected along the Swedish coast, of which 97 were pups born in that year, 12 subadults and 13 adults (Härkönen *et al.* 2008).

Clinical observations included a dorsally misshaped silhouette with an intermittent hump formation in the shoulder region, and restricted movement. In the final stage, animals showed respiratory distress and coughing up blood.The results of post-mortem examinations (complete necropsy of 16 seals and investigations of the respiratory tract and spleen of 85 additional

seals) revealed emphysema of the lung and mediastinum (Härkönen *et al.* 2008). Preliminary histopathological findings in 4 of the seals displayed multifocal acute catarrhal bronchitis, chronic interstitial pneumonia, severe atelectasis, moderate follicular hyperplasia and acute lymphocytolysis.

Bacteriological investigations of the lung and spleen of 3 harbour seals revealed untyped Gram-negative, biochemically inactive rods. Attempts to amplify PDV-specific RNA in lung tissues by conventional PCR, targeting the nucleocapsid and phosphoprotein genes and real-time PCR assays for PDV targeting the haemagglutinin protein gene, were negative. It was suggested that the epizootic most likely was caused by an unknown virus. As harbour porpoises found on the Swedish coast in the same year showed similar pathological findings, a cross-species infection could not be ruled out (Härkönen *et al.* 2008).

Mass-mortalities with unknown causes reported from the United States

Several smaller mortality events occurred on the coasts of the United States in the past 17 years (Gulland and Hall 2007). During each event between 24 and 34 harbour seals were found dead on both the west and the east coast.

In most cases pneumonia was found and a viral cause, such as morbillivirus or Influenza virus, was suspected from the histological lesions and the epidemiology but could not be proven. Different infectious agents were isolated from individuals found dead in New Jersey in 1991, such as *Erysipelothrix rhusiopathiae* and *Orthopoxvirus*. In harbour seals found dead on the coast of California in 1997, *Pseudomonas aeruginosa* was isolated, associated with pneumonia (Gulland and Hall 2007). The roles of these bacteria in causing mortality remain unclear.

SUMMARY

The published data shows that die-offs of harbour seals are recurrent events but are mainly reported from the waters of the United States and Europe. The causes of the epizootics so far have been mainly viral infections. For some events the source of infection remains unclear, but bacterial and viral infections were suspected. In other marine mammalian species, causes of mass mortalities have been biotoxins, parasites, human interactions, oil spills and changes in oceanographic conditions (Geraci *et al.* 1999, Gulland and Hall 2007).

An indirect contributing role on epizootics by anthropogenic activities, such as chemical pollution, has been shown in different studies (Ross 2002). Mortality rates vary strongly between causes, years and regions. However, it is clear that as a basis for the detection and understanding of epizootics a good monitoring programme with detailed investigations is needed. This programme would allow early detection of mortality rates above normal fluctuations, abnormal cause of death as well as isolation, identification and characterization of infectious agents, such as parasites, bacteria and viruses. Established systems can exclude or identify new as well as known causes for mass mortalities.

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