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Review article

Morbillivirus infections in aquatic mammals

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Summary — Infections with morbilliviruses have caused heavy losses among different populations of aquatic mammals during the last 5 years. Two different morbilliviruses were isolated from disease outbreaks among seals in Europe and Siberia: phocid distemper virus-1 (PDV-1) and phocid distemper virus-2 (PDV-2) respectively. PDV-1 was characterized as a newly identified morbillivirus, most related to canine distemper virus (CDV), whereas PDV-2 most probably is a strain of CDV. Morbilliviruses were also isolated from porpoises – porpoise morbillivirus (PMV) – and dolphins – dolphin morbillivirus (DMV) – which had stranded on the coasts of Europe. PMV and DMV proved to be closely related to, but distinct from 2 ruminant morbilliviruses, rinderpest virus (RPV) and *peste-des-petits-ruminants* virus (PPRV). Serological surveys carried out among pinniped and cetacean species in the seas of Europe and North America indicated that infections with these newly discovered morbilliviruses or closely related viruses commonly occur among aquatic mammal species.

morbillivirus / aquatic mammals / seals / dolphins

Résumé — Infections des mammifères aquatiques dues à des morbillivirus. *Les infections par des morbillivirus ont provoqué des pertes importantes parmi diverses populations de mammifères aquatiques au cours des 5 dernières années. Deux morbillivirus, désignés respectivement PDV-1 et PDV-2 (PDV =* phocid distemper virus*), ont été isolés à l'occasion de manifestations épizootiques de la maladie chez des phoques en Europe et en Sibérie. PDV-1 a été caractérisé comme étant un morbillivirus nouvellement identifié, fortement apparenté au virus de la maladie de Carré du chien, tandis que PDV-2 est plus probablement une souche de virus de la maladie de Carré du chien. Des morbillivirus ont été également isolés chez des marsouins et des dauphins échoués sur les côtes européennes. Le virus du dauphin et celui du marsouin se sont avérés très proches mais distincts*

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de 2 morbillivirus des ruminants, le virus de la peste bovine et le virus de la peste des petits ruminants. Des enquêtes sérologiques réalisées chez les espèces de pinnipèdes et de cétacés des mers européennes et nord-américaines ont montré que des infections par ces morbillivirus nouvellement découverts ou des virus très proches apparaissent couramment chez les mammifères aquatiques.

morbillivirus / mammifère aquatique / phoque / dauphin

INTRODUCTION

To date at least 18 different viruses belonging to 10 virus families have been identified in wild and captive aquatic mammals. Some of these viruses were found in seriously diseased animals, whereas others were isolated from animals not suffering from a particular disease. Although the host range of a number of the viruses detected in aquatic mammals seems limited to pinniped or cetacean species, other viruses are identical or closely related to viruses which occur in terrestrial mammals (for review see Visser *et al,* 1991). During recent outbreaks of infectious diseases in seals and dolphins in Europe, which killed thousands of animals, several "new" viruses were recognised and studied in detail. The emergence of these viruses was probably due to the profound immunosuppression caused by morbillivirus infections, which proved to be the primary cause of the outbreaks and may have predisposed the animals to secondary and reactivated infections (McChesney and Oldstone, 1989).

Although epizootics among aquatic mammals due to virus infections have been described before, none of the infections known thus far had caused such devastating effects on populations as the morbillivirus infection that struck the harbour seal *(Phoca vitulina)* population of Europe in 1988. Before this outbreak, 4 morbilliviruses had been recognised in terrestrial mammals. Under natural conditions these viruses were known to infect members of different mammalian orders: measles virus (MV) in humans, canine distemper virus (CDV) in dogs and other carnivores, rinderpest virus (RPV) and peste-des-petits-ruminants virus (PPRV) in artiodactyls (table I) (Pringle *et al,* 1991).

MORBILLIVIRUS INFECTIONS IN PINNIPEDS

In 1988, an outbreak of a serious apparently infectious disease started to spread among the harbour seals *(Phoca vitulina)* and with generally less severe disease signs also among the grey seals *(Halichoerus grypus)* of northwest Europe. The first cases were observed in the Kattegat in Denmark. Subsequently, seal populations of the North Sea, the Wadden Sea and the Baltic Sea became affected. The mortality among harbour seals was extremely high and even exceeded 80% in certain areas. By the end of 1988, > 17 000 seals had died. At different locations and times during the outbreak, the disease presented itself in different forms which led to speculation that more than one disease entity was responsible for the mass mortality in seals (Kennedy *et al,* 1989). The first indication that a morbillivirus infection was the primary cause of the outbreak came from a serological study, in which paired serum samples from affected animals were tested in a CDV neutralisation test (Osterhaus and Vedder, 1988). On the basis of these serological data and

Table I. Species susceptible to infection with different morbilliviruses.

	Natural infection			*Experimental infection*	
	Domestic species	*Wild species*		*Domestic species*	*Wild species*
MV	Humans Primates	(Primates)		Macaques Marmoset Mouse Hamster Rat	
RPV	Cattle Buffalo Pig Goat/sheep	(African) Buffalo Eland Giraffe Kudu Warthog Wildbeest	(Asian) Banteng Blackbuck Gaur Nilgai Sambhar	Cattle Rabbit	
PPRV	Goat/sheep	Gazelle Ibex Gemsbok		Goats Cattle Pig	Deer
PMV		Porpoise		Cattle Sheep/goat Dog	
DMV		Dolphins		Cattle Sheep/goat Dog	
CDV	Dog	Canidae Mustellidae Procyonidae	(*eg* fox) (*eg* ferret) (*eg* raccoon)	Dog Mouse Rat/hamster Mink Pig Cat	Ferret
PDV		Seal		Dog Mink	Seal

MV: Measles virus; RPV: rinderpest virus; PPRV: peste des petits ruminants virus; PMV: porpoise morbillivirus; DMV: dolphin morbillivirus; CDV: canine distemper virus; PDV: phocid distemper virus.

the observed clinical signs, which were similar to those in dogs with distemper, it was concluded that CDV or a closely related morbillivirus was the primary cause of the outbreak (Osterhaus *et al,* 1988). The virus was subsequently isolated from organs of dead animals and tentatively named phocid distemper virus-1 (PDV-1). It was shown that SFP dogs could be experimentally infected with this virus and the

animals developed mild clinical signs and CDV neutralising serum antibodies upon infection (Visser *et al,* 1990). After the identification of this morbillivirus infection as the primary cause of the disease outbreak in European harbour seals, a similar epizootic among Lake Baikal seals *(Phoca sibirica)* in Siberia, which had killed thousands of seals in 1987, was also attributed to infection with a morbillivirus. Affected animals developed disease signs similar to the PDV infected harbour seals, histopathological lesions indicative of a morbillivirus infection and also CDV neutralising serum antibodies were demonstrated (Grachev *et al,* 1989; Osterhaus *et al,* 1989). SPF dogs infected with organ material from these Lake Baikal seals developed mild clinical signs and CDV neutralising serum antibodies (Visser *et al,* 1990). A morbillivirus was isolated from organ material of the Lake Baikal seals, which was tentatively named phocid distemper virus-2 (PDV-2). PDV-1 and PDV-2 were adapted to grow in Vero cells, in which they caused cytopathic changes. PDV-1, PDV-2 and CDV were compared with respect to their biological, morphological, physical, protein chemical, and antigenic properties (Visser *et al,* 1990). From these studies it was concluded that PDV-1 should be considered a new member of the genus Morbillivirus, distinct from PDV-2 and CDV. In contrast, PDV-2 and CDV proved to be closely related if not identical viruses. These conclusions were predominantly based on the M_rs of viral proteins in western blot analysis, cross-reactivity patterns of serum antibodies from experimentally and naturally infected animals and on the reactivities of these viruses with panels of monoclonal antibodies raised against CDV.

These findings were confirmed by nucleotide sequence analyses of the NP, P, M, H and F genes of PDV-1 and the F gene of PDV-2 (Haas *et al,* 1991; Kövamees *et al,* 1991; Blixenkrone-Möller *et al,* 1992a; Sharma *et al,* 1992; Visser *et al,* 1992). The genes encoding PDV-1 Fo and H showed the highest degree of similarity to the analogous genes of CDV, 84 and 74% amino acid sequence similarities, respectively. Also the M, NP and P proteins showed the highest levels of similarity to their CDV analogues (67, 84 and 76%, respectively) when a comparison was made between the amino acid sequences of these proteins of the respective morbilliviruses (Blixenkrone-Möller *et al,* 1992a; Sharma *et al,* 1992). Comparison of the nucleotide sequence of the PDV-2 F gene with other morbillivirus F genes for which sequence data are available revealed a 91% similarity to the complete CDV F gene and a 97% similarity when only the Fo coding regions were compared. This indicated that PDV-2 and CDV were closely related if not identical (Visser *et al,* submitted). This level of sequence variation is similar to that observed between different isolates of rinderpest (Barrett *et al,* 1991). However, more nucleotide sequence data and antigenic cross-reactivity patterns of different strains of CDV and CDV-like viruses should be compared before it can be definitely concluded whether or not PDV-2 should be considered a strain of CDV.

During the PDV-1 outbreak among harbour seals, there proved to be an urgent need for a vaccine which could protect against phocid distemper in rehabilitation centres, aquaria and for certain isolated groups of seals of particular value. In the absence of a suitable large-scale production system for PDV-1 and in the light of the close antigenic relationship with CDV, we considered the use of CDV vaccines for this purpose. The vaccines currently used to prevent CDV infection in dogs are almost all live attenuated vaccines. Because of the inherent danger of insufficient attenuation and uncontrolled spread among other wild animal species, the use

of these attenuated vaccines is not recommended for wild animals (Appel, 1978). Inactivated morbillivirus vaccines have not been very successful in inducing adequate protection against disease (for review see De Vries and Osterhaus, 1993). Therefore (analogous to an experiment conducted in SPF dogs (De Vries *et al,* 1988), we have tested 2 inactivated CDV vaccines – an adjuvanted whole inactivated CDV and a subunit immune stimulating complexes (iscom) vaccine – for their ability to induce protective immunity against PDV-1 infection in seronegative harbour seals. After 3 vaccinations, resulting in the induction of CDV virus neutralising (VN) serum antibodies, 6 vaccinated and 2 sham-vaccinated animals were challenged with an organ suspension prepared from seals that had died from phocine distemper. The vaccinated animals proved to be protected from this challenge, which killed the 2 sham-vaccinated harbour seals (Visser *et al,* 1989). The subsequent introduction of the CDV-iscom vaccine for routine vaccination of seals admitted to a rehabilitation centre in The Netherlands indicated that this vaccine did induce adequate protection from phocine distemper. However, we also showed that although these animals were protected from developing phocine distemper, they were not fully protected from infection with PDV-1, and some of them developed mild respiratory disease signs upon PDV-1 infection (Visser *et al,* 1992). We speculated that this PDV-1 infection of the respiratory tract in CDV-iscom vaccinated seals would then be followed by a lifelong protection from phocine distemper (Visser *et al,* 1992). Collectively, the vaccination studies in the harbour seals reconfirmed that infection with the newly identified PDV-1 should be considered the primary cause of the epizootic in seals of northwest Europe that started in 1988.

MORBILLIVIRUS INFECTIONS IN CETACEANS

The first indication of the presence of a morbillivirus infection in cetacean species came from the demonstration of morbillivirus antigen in the organs of harbour porpoises that died along the Irish coasts during the PDV-1 outbreak among harbour seals in 1988 (Kennedy *et al,* 1988). In 1990, we isolated a morbillivirus from harbour porpoises which had died in the Dutch Wadden Sea (Visser *et al,* 1993). Also in 1990, a dolphin morbillivirus (DMV) was isolated from Mediterranean striped dolphins *(Stenella coeruleoalba)* during a mass mortality that started in the western part of the Mediterranean Sea and spread eastward *via* the French, Italian and Greek areas of this sea (Domingo *et al,* 1990; Van Bressem *et al,* 1991). The disease reached the dolphins of the Turkish coast in 1992 (unpublished observation). We have now obtained DMV isolates from organs of several stranded dolphins. Using an ELISA that detects morbillivirus antigen in organs, and by demonstrating VN antibodies in serum samples we showed that the majority of the stranded striped dolphins in the Mediterranean Sea had suffered from infection with a morbillivirus identical or closely related to our DMV isolates (Van Bressem *et al,* in press). Evaluation of the antigenic relationship between DMV, the porpoise morbillivirus (PMV) and other morbilliviruses indicated that DMV and PMV are closely related, and might belong to the same morbillivirus serotype. Phylogenetically these 2 viruses are both antigenically and genetically most related to the ruminant morbilliviruses RPV and PPRV. *In vitro* infection experiments in cells from different animal species and *in vivo* infection experiments in ruminants and dogs respectively showed biological differences between DMV and PMV. Ruminants proved to be susceptible to experi-

mental infection with both viruses, which both caused transient leukopenia. Dogs could also be infected experimentally with DMV and PMV. Pre-exposure to DMV or PMV protected the dogs from developing CDV viraemia and clinical signs upon challenge infection with virulent CDV (Visser *et al,* 1993). The close relationship between DVM and PVM was confirmed by nucleotide sequence analysis of a PCR product amplified by using a "universal" morbillivirus primer set, based on highly conserved regions of the morbillivirus P gene, surrounding the RNA editing site. Comparison of the nucleotide sequence of this region of the P gene confirmed that DMV and PMV are closely related viruses, quite distinct from all other members of the group, which form a distinct lineage phylogenetically more closely related to the ruminant than to the carnivore morbilliviruses (Barrett *et al,* 1993).

The present knowledge of susceptibilities of different animal species to natural and experimental infection with different morbilliviruses is summarized in table I.

EPIZOOTIOLOGY OF MORBILLIVIRUS INFECTIONS IN AQUATIC MAMMALS

Since the first outbreaks of mass mortality among pinniped species in northwest Europe and Siberia were attributed to morbillivirus infections (Osterhaus and Vedder, 1988; Grachev *et al,* 1989; Osterhaus *et al,* 1989), we and others have speculated about the origin of these viruses. Suggestions were made about a possible spillover of CDV from infected sledge dogs in Greenland to harbour seals in 1988 (Dietz *et al,* 1989; Osterhaus *et al,* 1989). This now seems highly unlikely since no reservoir for this virus, which is quite distinct from CDV (see above), has been identified among terrestrial mammals. The possibility of interspecies transfer of these viruses is, however, not unlikely as *eg* the outbreak of a PDV-1 infection in a mink farm in Denmark, probably resulted from contacts between mink and infected seals (Blixenkrone-Möller *et al,* 1992b). Our recent serological findings from serum samples collected from harbour seals and grey seals in Canadian waters from 1988–1991 indicate that a virus closely related or identical to PDV-1 was enzootic in healthy seals on the Canadian east coast before the outbreak started in northwest Europe (Ross *et al,* 1992). However, no disease signs indicative of a morbillivirus infection have even been reported from seals in this area. Another serological study that we recently carried out in the Arctic region in collaboration with R Zarnke (Department of Fish and Game, Fairbanks, State of Alaska), indicated that a PDV-1-like virus is also enzootic among several pinniped species without causing serious disease outbreaks or mass mortality in these seal populations (manuscript in preparation). One of the theories for the spread of PDV-1 from *eg* one of these arctic seal populations to the European seals is that harp seals *(Phoca groenlandica)* played a role as vector bridging the seal populations of Europe and North America (Dietz *et al,* 1989).

At present it is not clear whether or for how long the PDV-1 infection will persist in the seal populations of northwest Europe. We have recently found evidence that this virus has continued to spread among seals in the Dutch Wadden Sea and is circulating at the present time (Visser *et al,* submitted).

The virus (PDV-2) which infected Lake Baikal seals is more likely to have originated from a reservoir in terrestrial mammals. This virus proved to be closely related if not identical to CDV, and CDV infected local dogs were reported as the likely source of the outbreak (Grachev *et al,* 1989; Visser *et al,* 1990). Only comparison of the

nucleotide sequences of the locally-occurring CDV strains with those of PDV-2 and/or analysis of antigenic cross-reactivities would provide definite proof for this suggestion. A similar link between sledge dogs suffering from CDV infection and an outbreak of mass mortality among Crabeater seals *(Lobodon carcinophagus)* on the Antarctic continent in 1955, has been suggested (Bengston *et al,* 1991).

Screening of serum samples from dolphins and harbour porpoises of various species which stranded on the beaches of northwest Europe and the Mediterranean Sea ($n = 78$), for the presence of morbillivirus-specific VN antibodies showed that the majority of these animals ($n = 47$) had VN serum antibodies to morbilliviruses. These antibodies generally neutralised DMV and PMV equally well and were less effective in neutralising the ruminant and carnivore morbilliviruses. These data suggest that DMV and PMV, or closely related morbilliviruses are enzootic among several cetacean species.

The morbilliviruses found in dolphins (DMV) and porpoises (PMV) during recent years, probably do not have their origin in terrestrial mammals. Although these 2 viruses proved to be most related to the morbilliviruses of ruminants (RPV and PPRV), they should be considered a separate virus serotype. In this light it is interesting to note that phylogenetically the cetacean species are more related to ruminants (Martin, 1990) than the pinniped species, which are more related to the terrestrial carnivores (King, 1983). Consequently, the phylogenetic relationships between the morbilliviruses largely parallel those of their respective host species. In view of the differences in rapidity of evolutionary diversification between mammals on the one hand and viruses on the other hand, it seems highly unlikely that this parallel would be the result of a parallel evolution. It is more likely that common viral ancestors have acquired access to phylogenetically related animal species on the basis of biological similarities. Therefore it may be speculated that CDV and PDV-1 share a common morbillivirus ancestor. Although morbilliviruses are generally restricted to one mammalian order, it is also likely that DMV and PMV on the one hand, and RPV and PPRV on the other hand share a common morbillivirus ancestor.

CONCLUDING REMARKS

Different species of aquatic mammals have been infected with at least 4 different morbilliviruses during the last 5 years: PDV-1, PDV-2 (CDV), DMV and PMV. The introduction of these viruses into hitherto unexposed populations has propably been the reason for the severity and extent of the epizootics with the consequent massive losses. Other serious disease outbreaks among pinnipeds, which have been referred to as "infectious viral pneumonia", like those occurring among the Crabeater seals in the Antarctic in 1955 and among harbour seals along the east coast of the USA in 1979 and 1982 (Hinshaw *et al,* 1984; Bengston *et al,* 1991), may also have been associated with morbillivirus infections. Although the latter 2 outbreaks were attributed to influenza virus infections, it would be interesting to investigate whether or not these influenza viruses were indeed the primary cause, or the result of a morbillivirus induced immunosuppression resulting in a higher degree of susceptibility to these infections. This possibility is even more likely when we consider that the disease could not be reproduced by experimental infection with the isolated influenza viruses (Geraci *et al,* 1984). These morbillivirus infections could have been caused by CDV strains which spilled over from dogs or other terrestrial carnivores rather than PDV-1, as has been

suggested for the outbreaks among Crab-eater and Baikal seals (Grachev *et al*, 1989; Visser *et al*, 1990; Bengston *et al*, 1991). Also a possible spill-over of CDV vaccine strains, which are attenuated for dogs but pathogenic for wild carnivores should be considered. However, there is a new morbillivirus, which may properly be considered a genuine phocine distemper virus, which is closely related to CDV and which is not commonly found in terrestrial carnivores. This virus was shown to be enzootic among pinniped populations at the northern hemisphere. A similar situation exists for the morbilliviruses of cetacean species, like porpoises and dolphins. In some of these species, infections with morbilliviruses belonging to the DMV/PMV serogroup, which is most related to the ruminant morbilliviruses RPV and PPRV, appear to be enzootic. Although several of the morbillivirus outbreaks have caused heavy mortalities among pinnipeds and cetaceans, it may be that under normal conditions, where these viruses are enzootic, they will not constitute a serious threat to the survival of the aquatic mammal species concerned. However, seriously endangered species, like the Mediterranean and Hawaiian monk seals (*Monachus monachus* and *Monachus schauinslandi*) and the Finish Saimaa seal, of which only small numbers remain, may be even more threatened with extinction if their populations were struck by a morbillivirus infection.

To date it is not clear whether the recent morbillivirus infections in different species of aquatic mammals have been facilitated or aggravated by anthropogenic influences. These may have included over-fishing, resulting in excessive migratory movements, environmental pollution, causing malfunction of the immune system, or other disturbances of the natural habitat of these species, caused by humans or their domestic animals.

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