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Transmission of morbilliviruses within and among marine mammal species

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Transmission of morbilliviruses within and among marine mammal species has been documented in a variety of marine habitats. Cetacean morbillivirus spreads between cetacean species in the aquatic environment whereas both phocine distemper virus and canine distemper virus have been associated with transmission within and between pinniped and terrestrial carnivore species in their natural habitat and at the aquatic–terrestrial interface. Periodically these viruses have caused large epizootics involving thousands of animals, due to sustained intra-species virus transmission. Social behavior of host species, marine habitat, geographical barriers and virus–host adaptations all likely contribute toward modulating virus spread. In combination with increased surveillance and whole genome sequencing, further research into ecological and host factors will be pivotal in better understanding the global transmission dynamics of marine morbilliviruses.

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Introduction

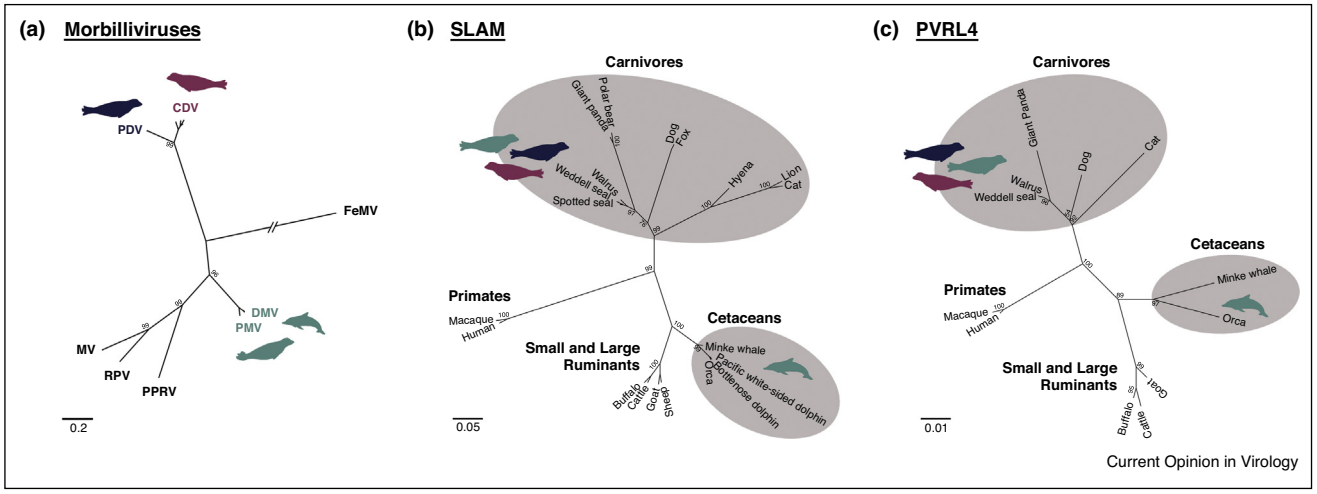
Intra-species transmission of epizootic viruses in marine mammal species is known to lead to periodic mass mortality events (MME) and together with circulating enzootic viruses serves as a source of potential inter-species transmission of viruses among aquatic and terrestrial mammals, including humans. In recent years, an increasing number of viruses have been shown to infect marine mammals, an advance largely driven by increased surveillance and the use of more advanced molecular diagnostic techniques [1–3]. Although such discoveries have improved our understanding of the evolution of virus genera, the cross-species threat posed by many of these newly discovered aquatic mammal viruses to terrestrial hosts requires further investigation due to some salient precedents. Marine caliciviruses, which affect pinniped and cetacean populations, can readily spread from aquatic to terrestrial hosts, as demonstrated by vesicular exanthema of swine, a disease which circulated in domestic pigs in the USA from 1932 to 1959 [4]. This virus was later found to be closely related to San Miguel Sea Lion Virus and is thus assumed to be of marine origin [5,6]. Sealpox viruses, which are enzootic in both true seals (*Phocidae* sp.) and eared seals (*Ottaridae* sp.), have also been reported to be transmissible to humans [7,8]. On a broader scale, epizootics of influenza viruses have been extensively documented in phocid populations [9], some of which have caused isolated spillover cases in humans [10]. Recent examples include the identification of influenza A H10N7 and H3N8 viruses as the cause of MMEs in harbor seals in the North Sea and New England, respectively [11,12]. However, amongst viral pathogens documented to infect marine mammals, morbilliviruses are considered to pose the highest risk due to a high propensity to cause large epizootics in susceptible cetacean and phocine species [13,14].

Morbillivirus transmission in the terrestrial and marine environment

The genus *Morbillivirus* within the family *Paramyxoviridae* is comprised of enveloped viruses that contain a single-stranded non-segmented negative sense RNA genome. There are currently seven members of this genus, measles virus (MV; humans and non-human primates), canine distemper virus (CDV; domestic dog and multiple wild carnivore species), recently eradicated rinderpest virus (RPV; domesticated cattle and large wild even-toed ungulates), peste des petits ruminants virus (PPRV; goats, sheep and small wild even-toed ungulates), phocine distemper virus (PDV; pinnipeds), cetacean morbillivirus (CeMV, cetaceans), and the recently identified feline morbillivirus (FeMV; domestic cats) (Figure 1a). Infections with morbilliviruses are characterized by severe systemic disease in infected hosts which can result in high levels of morbidity and mortality. This is largely due to the induction of generalized immunosuppression in the infected host, which can lead to bacterial or viral co-infections [15].

Three viruses from this genus — CeMV, PDV and CDV — have been linked to multiple large epizootics in marine mammal populations over the last three decades (Figure 2). CeMV is capable of inducing a severe and often fatal disease in a number of cetacean species

Figure 1



Phylogenetic analyses of morbilliviruses and its receptors SLAM and PVRL4. Protein sequences were analyzed by maximum-likelihood phylogenetic reconstruction with 1000 bootstrap replicates. JTT nucleotide substitution model was selected as best-fit model according to Bayesian information criteria. **(a)** Hemagglutinin protein of morbilliviruses. Each virus clade is represented by Virus: Country-Year_strain/species (Genbank accession No.): PDV: NL-1988_harbor-seal (KC802221), DE-2002_harbor-seal (KU342692), US-2006_harbor-seal (HQ007902), CDV: Onderstepoort (AF305419), RU-1988_baikal-seal (X84998), DE-1989_5804/dog (AY386315), CN-2014_panda (KP793921), FeMV: CN-2010_cat (JQ411016), CeMV: ES-1990_DMV/striped-dolphin (AY586536), ES-2007_DMV/pilot-whale (HQ829972), IT-2013_DMV/fin-whale (AY586536), IR-1988_PMV/porpoise (FJ648457), PPRV: IQ-2011_Kurdistan/goat (KF648288), RPV: KE-1910_KabeteO/cattle (X98291), MV: SD-1997_KS/human (HM439386). FeMV branch was truncated for graphical reasons (interrupted lines). **(b)** SLAM receptor protein of animal species associated to each morbillivirus. GenBank accession No.: Spotted seal (AB428368), Weddell seal (XM_006743440), Walrus (AB428369), giant panda (NW_003218810), polar bear (NW_007907182), dog (FJ626691), fox (EU678638), hyena (JN812974), lion (JN812972), cat (JN812973), Minke whale (XM_007171753), Pacific white-sided dolphin (AB428366), bottlenose dolphin (XM_004327846), Orca (AB428367), sheep (NM_001040288), goat (DQ228869), cattle (AF329970), water buffalo (DQ228868), macaque (AB742520), human (AY040554). **(c)** PVRL4 receptor protein of animal species associated to each morbillivirus. GenBank accession No.: Weddell seal (XM_006744413), walrus (XM_004407894), giant panda (XM_002928747), dog (NM_001313853), cat (XM_019822297), minke whale (XM_007171734), Orca (XM_004284416), goat (XM_005677185), cattle (NM_001024494), water buffalo (XM_006048495), macaque (AB742522), human (NM_030916). Representative images of host marine mammal species are located next to the relevant virus (a) or susceptible host species receptor (b and c) and are color coded according to the virus: PDV — blue, CDV — pink, CeMV — turquoise. Bootstrap values are presented on each node. Scale bar indicates nucleotide substitutions per site.

including striped dolphins (*Stenella coeruleoalba*) [14], bottlenose dolphins (*Tursiops truncatus*) [16] and fin whales (*Balaenoptera Physalus*) [17•]. PDV infects different phocid species, but epizootics have mostly been associated with infection of harbor seals (*Phoca vitulina*) [18••]. CDV primarily infects members of the order Carnivora with dogs, raccoons and foxes serving as key reservoir host species. Non-human primates (*Macaca* sp.) and species belonging to the orders Rodentia (marmots) and Artiodactyla (javelina), have also been reported to be susceptible to CDV [19]. Isolated outbreaks of CDV can occur in marine mammal species, with large epizootics documented in both Caspian seals (*Pusa caspica*) [20] and Baikal seals (*Pusa sibirica*) [21].

Morbilliviruses — cellular tropism and receptor usage

The morbillivirus genome encodes the nucleocapsid (N), the phosphoprotein (P/V/C), the matrix (M), the fusion (F), the hemagglutinin (H), and large (L) proteins. The N, P and L proteins form the ribonucleoprotein complex and mediate viral replication and transcription, the M protein facilities virus assembly and egress, the F glycoprotein fuses viral and cellular membranes while the H glycoprotein binds to cellular receptor(s) enabling entry into the host cell. Morbillivirus infections are characterized by a strong tropism to immune cells (e.g. B-lymphocytes and T-lymphocytes, macrophages, and dendritic cells), epithelial cells and in some cases neuronal cells. Virus spread to the central nervous system is commonly observed in CDV, PDV and CeMV infections, resulting in acute encephalitis [14,22,23] or long-term persistent infections [24]. Morbilliviruses entry into a susceptible host and subsequent systemic viremic spread relies on infection of immune cells expressing the cellular receptor signaling lymphocytic activated molecule (SLAM/CD150) [25]. In the later stages of the infection, morbilliviruses infect epithelial cells throughout the body via the use of poliovirus-receptor-like 4 (PVRL4/Nectin-4) which is expressed at adherent cell junctions [26]. This facilitates virus exit and further transmission to other hosts. Both receptors appear to be relatively conserved within species of the same order, as shown by the formation of monophyletic groups in the analyses of the amino