

Emerging viruses in marine mammals

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Abstract

Emerging infectious disease has become a serious concern that has consequences for human, animal and environmental health on a global scale. During the past two decades, it has become clear that viruses are emerging in terrestrial environments from the human–animal interface at an unprecedented rate. Thus, the understanding of complex diseases associated with emerging zoonotic pathogens and the creation and execution of strategies to deal with this issue has assumed new public health importance, requiring a One Health approach involving multiple health disciplines. Similar infectious disease trends involving emerging viruses are now being documented in aquatic ecosystems and are impacting marine mammals. As in terrestrial species, emerging viruses in marine mammals may be associated with neoplasia, epizootics and zoonotic disease and involve a complex pathogenesis involving noninfectious cofactors such as anthropogenic toxins, biotoxins, immunologic suppression and other environmental stressors. Among the viruses recently isolated from marine mammals are influenza viruses, morbilliviruses, papillomaviruses, herpesviruses, arboviruses, caliciviruses and others. Many of these emerging marine mammal viruses are associated with disease and specific pathologic findings. In other cases, the disease significance of these novel viruses is unknown and requires further research. In this report, we briefly review emerging viruses that have disease significance for marine mammals and/or public health. Novel concurrent clinicopathologic data will be presented when available broadening the understanding of disease pathogenesis. References will help provide more in-depth information. Additionally, this review has demonstrated that marine mammals may be important sentinel animals that indicate environmental health concerns and parallel emerging public health issues.

Keywords: Marine mammals, Emerging viruses, Sentinel species, Zoonotic disease, One Health initiative

Review Methodology: The following databases were searched: CAB Abstracts, Medline and Agricola (keyword search terms used). Additionally, references from publications obtained by this method were used to check for relevant supplemental material. Colleagues were also contacted to confirm upcoming studies not yet published.

Introduction

In the past 20 years, emerging infectious disease (EID) has become a complex and serious concern that has consequences for human, animal and environmental health on a global scale [1–3]. By broad definition, EID may be associated with infectious agents that are newly identified, previously identified and spreading to a new population and/or spreading to a new geographic region that is

undergoing ecologic transformation. Contributing factors to the increased incidence of EID include microbial adaptation, host immunologic dysfunction, expansion of the human population and consequent environmental degradation, climatic changes resulting in shifts in zoonotic vectors and the negative synergistic effects of EID and other infectious and non-infectious diseases. Importantly, three-fourths of all EIDs of humans are zoonotic, most originate in wildlife, and their incidence is increasing [2, 4].

Thus, the understanding of complex diseases associated with emerging zoonotic pathogens and the creation and execution of mitigation strategies to deal with this issue has assumed new public health importance and requires a One Health approach of working across disciplines involving human, domestic animal, wildlife and environmental health [2, 5].

Similar infectious disease trends involving emerging viruses are now being documented in aquatic ecosystems and are impacting marine mammals. In particular, the detection and characterization of viruses in marine mammals have increased considerably in the past 10 years. As in terrestrial species, emerging viruses associated with disease in marine mammals may be associated with neoplasia, epizootics, zoonotic disease and involve a complex pathogenesis including noninfectious cofactors such as anthropogenic toxins, biotoxins, immunologic suppression and other environmental stressors [6–9]. Advanced biotechnologies combining virus isolation and molecular diagnostics have greatly enhanced the ability to identify potential disease aetiologies occurring in marine mammals and the impact these diseases have on individuals, populations and the ecosystem as a whole [10]. However, in some instances it is difficult to make a causal association between newly reported marine mammal infectious agents and a clinical presentation or pathology due to inconsistencies in marine mammal morbidity/mortality investigative effort and the logistical and economic limitations for adequate pathologic investigations. Thus, the significant advances in diagnostic methodology that have allowed the improved detection of potential pathogens have to be carefully interpreted in relation to pathologic findings which support a causal impact on morbidity or mortality. This paper will provide a general overview of emerging viruses that have disease significance for marine mammal and/or public health. Concurrent clinicopathologic data will be presented when available that will help broaden our understanding of viral disease pathogenesis in various marine mammal species. In cases of emerging novel viruses with no established or associated disease significance, references will be provided for further study. In-depth discussions of clinical signs, therapy, diagnosis and epidemiology will also be available in supplied references. Additionally, the application of some marine mammal species as a sentinel species for environmental health concerns and emerging public health issues will be discussed [2, 11–13].

Papillomaviruses

The family Papillomaviridae includes 48 genera of double-stranded circular DNA viruses that infect epithelial cells of mucosal and cutaneous locations [7, 14]. Papillomaviruses (PVs) are typically species-specific, site-specific and display a predilection for squamous epithelium causing benign sessile plaques or verrucous papillomas or, less commonly,

malignant neoplasia [15]. Novel PVs have recently been reported by molecular, immunohistochemical and/or classical microscopic techniques associated with sessile, verruciform and papular cutaneous and genital papillomas in various marine mammal species including bottlenose dolphins (*Tursiops truncatus*) [16, 17], killer whale (*Orcinus orca*) [18], sperm whale (*Physeter macrocephalus*) [19], West Indian manatee (*Trichechus manatus*) [20, 21], harbour porpoise (*Phocoena phocoena*) [22], Burmeister's porpoise (*Phocoena spinipinnis*) [23] and California sea lion (*Zalophus californianus*) [24]. Gastric papillomas associated with papilloma-like virions are also reported in beluga whales [25].

The Florida manatee (*T. manatus latirostris*) is a subspecies of the West Indian manatee and is found in coastal southeastern marine, brackish and fresh water habitats of the United States. It is a threatened species which has a high annual mortality due to human-related factors such as boat impacts [26]. The manatee immune system appears highly developed to protect it against pathogens with naturally occurring infectious disease uncommon [20, 26–28]. However, over the past decade, PV-associated papillomatosis has appeared in manatees which is the first viral disease reported in this species [29]. To date, four novel manatee papillomaviruses (TmPVs) have been identified in Florida manatees, two are cutaneotropic (TmPV1 and TmPV2) and two are mucosotropic (TmPV3 and TmPV4) and cluster in the *Rhopapillomavirus* genus [30]. TmPV1 is widely dispersed among manatees and genetically similar to close-to-root forming verruciform to papular cutaneous papillomas [29, 31] while not much is known about TmPV2 [30]. The two mucosotropic PVs form sessile mucosal genital papillomas (TmPV3 and TmPV4) [21, 30, 32]. Both TmPV3 and TmPV4 are similar in size and in genomic characterization of all PVs, with one non-coding region and seven open reading frames (ORFs) including the E7 ORF which is absent in cetacean PVs [32]. Alternatively, TmPV3 and TmPV4 are the first known genital mucosotropic PVs in manatees presenting a suspected novel sexually transmitted viral disease in this species similar to the emerging PV-associated genital lesions in bottlenose dolphins (see below).

More recently, and for the first time, G-quadruplex (G4) sequences have been identified and characterized in a PV infecting a non-human. DNA sequences with the potential to form G-quadruplex structures (G4) were identified across the three manatee PV genomes (TmPV1, TmPV3 and TmPV4). G4 are associated with key biological functions in humans including the regulation of transcription and protein synthesis and the prevention and degradation of genomic instability. In all TmPVs, G4 sequences were located in the non-coding region near putative E2 binding sites. Based on the role of G4 in PVs of humans, these findings suggest that G4 in TmPVs are possible regulatory elements of protein synthesis [32].

Interestingly, clinicoimmunologic data suggest that the manatees with cutaneous tumours associated with TmPV1

are immunologically suppressed and that the papillomas result from activation of latent papillomavirus infections and re-inoculation from active infections [20]. Additionally, recent seroepidemiologic data [33] indicated that Florida manatees living in the wild are naturally infected by TmPV1 but rarely show TmPV1-induced papillomatosis. The prevalence of TmPV1 antibody among manatees with the absence of lesions suggests an immunologic response that effectively controls productive PV infection and/or rapidly resolves lesions. Similar studies have not been conducted to evaluate the prevalence of TmPV3 and TmPV4 in wild manatees. The emergence of papillomavirus-induced papillomas in Florida manatees, the possibility of activation of latent infection or transmission of active infection to free-ranging manatees and the underlying cause(s) of immune suppression predisposing manatees to viral papillomatosis require future research for understanding the pathogenesis of this emerging viral infection.

Notably, in the past 12 years, nine novel bottlenose dolphins PVs (TtPV1–9) have been separately associated with genital papillomatosis and characterized by phylogenetic analysis within the genera *Omikronpapillomavirus* (OmikronPV), *Upsilonpapillomavirus* (UpsilonPV) and *Dyopipapillomavirus* [7, 16, 17, 34, 35]. Two delphinid gammaherpesviruses (DeHV-4 and –5) have also been found with PV co-infections [36, 37]. Orogenital sessile papillomas (OP) associated with novel PV and herpesvirus (HV) infections were first noted in wild bottlenose dolphins from southeast Atlantic coastal waters in 2005 as part of a capture/release health assessment study from 2003 to 2015 [6, 38–40]. Lingual and genital mucosal lesions were all grossly and microscopically similar sessile papillomas [40]. A novel PV was isolated from a genital papilloma which was designated as TtPV-2 [16]. This virus represented the first identified North American cetacean PV associated with a genital sessile papilloma. Electron microscopy revealed the presence of HV-like intranuclear particles and enveloped cytoplasmic virions in all lingual and genital papillomas examined [38]. Polymerase chain reaction (PCR) analyses also detected the presence of DeHV-4 in the genital papillomas while serological screening using an antibody-based TtPV enzyme-linked immunosorbent assay (ELISA) demonstrated previous and/or current infection of the DeHV-4 positive dolphins with at least one TtPV type [37, 41]. The TtPV ELISA was also used to assess the extent of dolphin PV infection [42]. Ninety percent of wild adult dolphins sampled were antibody positive with a male bias and evidence for seroconversion with age. Interestingly, 76% of seropositive dolphins did not have genital tumours [41]. Dolphins with OP also had clinicopathologic abnormalities including hypoferraemia, hyperglobulinaemia and hyperalphaglobulinaemia associated with an acute phase inflammatory response and upregulated innate and humoral immunity likely responses to the tumours and/or the viruses associated with the tumours [43]. No human health risks are known to exist from marine mammal PVs or HVs.

The prevalence of OP increased dramatically during the first 3 years of the aforementioned dolphin health assessment study, supporting laboratory data that an infectious agent(s) was driving disease emergence [6]. The data indicated that PV/HV infection in the wild dolphins examined is common and readily transmitted horizontally, most likely through sexual contact [41, 43]. The absence of tumours in PV antibody positive dolphins suggests previous PV infection with immunologic suppression of tumour formation. This speculation is further supported by the noted eventual disappearance of some OP on subsequent follow-up health assessment examinations. However, the viral component in tumour pathogenesis appears to be complex since PV DNA is not always detected after infection and neoplastic transformation [37]. These observations suggest that genital papillomatosis is an endemic self-limiting disease in free-living dolphin. However, the biologic behaviour of OP is less clear as it appears that lesions in captive dolphins can undergo malignant transformation and progress to life-threatening aggressive metastatic squamous cell carcinoma [38, 43, 44]. Further research is needed to determine whether this occurs in free-living dolphins.

This research showed the first evidence of tumour-associated combined PV and HV-infection in a marine mammal species and evaluated the controversial effects of viral co-infection in tumour pathogenesis. The latter is an important comparative issue of human health significance as some human PVs are the causative agents of cervical carcinoma and are regularly found with herpes simplex virus type-2 co-infections [37].

The role of PVs as pathogens in wild pinnipeds is currently unknown. A novel PV species (ZcPV1) was isolated from cutaneous prepuccial and axillary benign proliferative lesions from two captive adult California sea lions [24]. Both lesions regressed spontaneously after 2–5 months. Additionally, multiple cutaneous proliferative sessile plaques have been recently reported in another captive California sea lion that were associated with ZcPV1 which progressed to *in situ* and invasive squamous cell carcinoma [45]. ZcPV1 is in a clade with canine papillomavirus (CPV3, CPV4) in the genus *Chipapillomavirus* [46].

Paramyxoviridae: Morbilliviruses

For in-depth references and recent reviews of marine mammal morbilliviruses see Duignan *et al.* [46–48], Van Bressema *et al.* [49] and Bossart *et al.* [2, 6, 50].

The family Paramyxoviridae includes the important marine mammal viral pathogens in the *Morbillivirus* genus which includes canine distemper virus (CDV), phocine distemper virus (PDV) and cetacean morbillivirus (CeMV). Other viruses in this genus include measles virus (MV) in humans and primates, peste-des-petits ruminant virus in small ruminants and rinderpest virus in large ungulates. The marine mammal morbilliviruses emerged as recognized

viral pathogens in the late 1980s. PDV and CDV are transmitted at the aquatic–terrestrial interface while CeMV is transmitted between cetacean species in the aquatic environment. Periodically, marine mammal morbilliviruses cause widespread mass mortalities due to uninterrupted virus transmission that is further influenced by unique social behaviours, environmental factors and virus–host variations such as immunologically naive populations or those populations with low levels of herd immunity [51]. CDV is documented causing epizootics in Baikal seals (*Pusa sibirica*) and Caspian seals (*Pusa caspica*). Harbour seals (*Phoca vitulina vitulina*) are the most susceptible phocids to PDV based on historic epizootics and immune function studies [52, 53]. The reason for this susceptibility is unknown. Data suggest that the harbour seal immune system recognized fewer PDV antigens than that of grey seals [52]. Odobenidae (walrus) and Otariidae (sea lions and fur seals) historically do not appear to be highly susceptible to PDV. CeMV appears to be endemic in pilot whales (*Globicephala* sp.) of the North Atlantic with a high level of herd immunity in these species with only sporadic mortality [49, 54]. However, CeMV has caused mass epizootics in other odontocetes including harbour porpoises (*P. phocoena*) and striped dolphins (*Stenella coeruleoalba*) in Europe in the late 1980s and early 1990s. Between 1987 and 1988 an epizootic of CeMV infection with widespread mortality occurred in bottlenose dolphins along the eastern coast of the United States [55]. Approximately 2500 dolphins died, representing a ten-fold increase in mortality and loss of an estimated 50% of the inshore population of bottlenose dolphins [56]. Deaths were reported from New Jersey to central Florida [57]. While this epizootic was unprecedented in scale, it was preceded and followed by more localized die-offs of bottlenose dolphins on the US Atlantic coast and in Gulf of Mexico [47, 55, 58]. Recently, another large epizootic of CeMV infection began along the eastern US seaboard which moved southwards in a similar pattern to the 1987 epizootic killing approximately 1650 dolphins from 2013 to 2015 [59, 60]. Additionally, CeMV has recently emerged in the Southern Hemisphere as a cause of epizootics among several delphinid species in Australia and Brazil [61–65]. Globally, CeMV infection has now been detected in many species of odontocetes (toothed whales and dolphins) and some mysticetes (baleen whales). For example, CeMV has recently been reported in stranded fin whales (*Balaenoptera physalus*) from the Mediterranean and North Sea [66, 67]. The taxonomy of CeMV currently is characterized by four strains and two lineages which are reviewed in Duignan *et al.* [46].

Antibodies to CeMV have been found in Florida manatees and polar bears (*Ursus maritimus*) without clinicopathologic evidence of disease [28, 68]. Similarly, there is preliminary evidence of CDV infection in northern (*Enhydra lutris kenyoni*) and southern sea otters (*Enhydra lutris nereis*) from the Pacific Northwest and California [46]. Alaskan sea otters may have been infected from a phocine

distemper like virus rather than CDV [69] while no evidence of infection or disease has been reported in marine otters (*Lontra felina*) from Chile and Peru.

Marine mammal morbilliviruses as with terrestrial morbilliviruses have an affinity for lymphoid, epithelial and neuronal tissue and the pathologic findings of CeMV and PDV are similar to CDV infections of terrestrial carnivores [70, 71]. Lymphotropic morbillivirus replication results in immunosuppression and often secondary opportunistic bacterial, fungal and protozoal infections which may result in highly variable lesions in more chronic morbillivirus infections [6, 72, 73]. Pathologic findings of infection include interstitial to bronchointerstitial pneumonia, profound widespread lymphoid depletion and syncytial cell formation [46, 74]. Phocids may also develop severe interstitial emphysema. Additionally, cetaceans with chronic morbillivirus infection may develop nonsuppurative encephalitis [75]. Intracytoplasmic and intranuclear eosinophilic viral inclusions may be detected within bronchial and bronchiolar epithelial, pulmonary syncytial, neuronal and other cell types. These inclusions, along with lymphoid and other tissue, are often found to be immunohistologically positive for morbillivirus antigen. No human health risks are known to exist from CeMV, PDV and CDV.

Important unanswered questions remain regarding the epidemiology of CeMV infection including the maintenance of CeMV infection in cetacean populations during inter-epidemic periods and the factors that lead to clinical disease and the development of epizootics. Recently, one author (GDB) and colleagues reported novel seroepidemiologic and pathologic evidence of subclinical CeMV infection in a population of the wild Florida bottlenose dolphins as part of the long-term capture/release health assessment study described above [50]. Importantly, novel evidence for recurring CeMV infection was found in dolphins in the first post-CeMV epizootic (1987–1988) period in the absence of pathologic evidence widespread CeMV mortality [47].

To further investigate CeMV infection in the study dolphin population, a suite of clinicoimmunopathologic variables was evaluated in dolphin seropositive for CeMV and seronegative healthy dolphins [71]. In CeMV seropositive dolphins, innate immunity was upregulated with significant increases in lysozyme concentration and marginally significant increases in monocytic phagocytosis. Adaptive immunity was also affected. Mitogen-induced T lymphocyte proliferation responses were significantly reduced in dolphins with positive CeMV antibody titres and marginally significant decreases were found for absolute numbers of CD4 lymphocytes. The findings suggested impairment of cell-mediated adaptive immunity, similar to the immunologic pattern reported with acute morbillivirus infection in other species (e.g. human measles, canine distemper) [71]. These data indicated that exposure to CeMV may result in subclinical infection producing immunologic changes that could influence overall health. The cell-mediated immunosuppressive effects associated

with subclinical CeMV infection could make this dolphin population highly susceptible to opportunistic infectious and noninfectious diseases. Thus, the long-term impact of emerging viral diseases on population health may be difficult to appreciate when dealing with a short-term mortality-associated epizootic from an emerging virus. For example, morbilliviruses and some PVs are thought to interfere with population health by various mechanisms including impacts on population abundance by increased mortality rates, lowered reproductive success, compromised immunity or by synergistically increasing the virulence of other diseases [2, 43, 50, 76, 77].

Paramyxoviridae: Respirivirus (Parainfluenza Viruses)

A parainfluenza virus (TtPIV-1) was isolated from a captive bottlenose dolphin which was determined to be related to bovine PIV-3 genotype B [78, 79]. A serologic survey demonstrated antibodies to parainfluenza in wild and captive bottlenose dolphins [80]. Seroconversion to TtPIV-1 also occurred in other exposed dolphins. Postmortem pathologic findings in this dolphin included focally extensive pyogranulomatous bronchointerstitial pneumonia and ulcerative laryngotracheitis but the role of TtPIV-1 in these is unknown. TtPIV-1 is a potential zoonosis as its relative, PIV-3, can infect terrestrial mammals including humans [46].

Influenza Viruses

For comprehensive reviews and zoonotic discussion of influenza viruses see Fereidouni *et al.* [81], Duignan *et al.* [46] and Bailey *et al.* [5]. Influenza viruses are members of the orthomyxovirus family and classified into four types: A, B, C and D. Only influenza A and B viruses are found in marine mammals. Antigenic shifts within influenza A viruses contribute to the emergence of new viral strains. Harbour seals are especially impacted by influenza A and B viruses [46, 82]. Epizootics causing mass mortalities among harbour seals have been associated with numerous influenza A strains in the eastern and western North Atlantic and North Sea including a large die-off in 2014 [83]. Seroepidemiologic studies indicate that influenza A viruses including pandemic influenza H1N1 commonly infect other healthy wild pinnipeds globally including California sea lions, northern sea otters, northern elephant seals (*Mirounga angustirostris*), harp seals (*Pagophilus groenlandicus*) and hooded seals (*Cystophora cristata*), and cetaceans including common minke whales (*Balaenoptera acutorostrata*), Dall's porpoises (*Phocoenoides dalli*) and beluga whales (*Delphinapterus leucas*) [84–88]. Two influenza A strains were isolated postmortem from a long fin pilot whale (*Globicephala melas*) [89] and one influenza A strain was isolated from an unidentified orca [90].

Phylogenetic research indicates that many of the marine mammal influenza A strains originated from aquatic avian strains [5].

While various hosts for influenza A viruses are well documented, influenza B viruses have been demonstrated in only humans and seals [91]. Influenza B virus has been routinely detected in healthy harbour and grey seals (*Halichoerus grypus*) from the North Sea for almost 20 years [91, 92]. Serological evidence for influenza B infection has also been detected in Caspian seals (*P. caspica*) and South American fur seals (*Arctocephalus australis*) [93, 94].

Gross and microscopic lesions of influenza A in harbour seals include acute haemorrhagic interstitial pneumonia with necrotizing bronchitis-bronchiolitis, regional haemorrhagic lymphadenopathy, subcutaneous emphysema, acute conjunctivitis and suppurative to serosanguinous rhinitis [46, 82, 95]. It is unclear whether influenza B causes clinical disease in seals [92].

From a public health perspective, influenza A viruses have pandemic potential with associated high human mortality. Influenza B viruses cause disease in the elderly and other high risk human populations. Thus, appropriate personal protective equipment and disinfection precautions should be encouraged when working with stranded and wild marine mammals that are susceptible to influenza infection and associated disease.

Polyomaviruses

Polyomaviruses have been isolated from a northern fur seal (*Callorhinus ursinus*), California sea lions, a Hawaiian monk seal (*Neomonachus schauinslandi*), a common dolphin (*Delphinus delphis*), a southern sea otter and a Weddell sea (*Leptonychotes weddellii*) [96–101]. A novel polyomavirus (sea lion polyoma virus 1) was identified from a proliferative tongue lesion of a California sea lion which the first known polyomavirus of a host in the order Carnivora [102]. California sea lion polyoma virus 1 infection was present in 24% of wild stranded sea lions as demonstrated by q-PCR. The association of these polyomavirus infections with pathology or disease is largely unclear at this time. The public health significance is unknown.

Arboviruses: Togaviridae and Flaviviridae

Several notable human and animal pathogens belong to the arthropod-borne virus (arbovirus) families Togaviridae and Flaviviridae. The Togaviridae zoonotic alphaviruses include Venezuelan, western and eastern equine encephalitis (EEE) viruses [103]. The Flaviviridae includes the dengue fever virus, yellow fever virus, West Nile virus, Zika virus and others and have notable recent public health implications [8]. West Nile virus infection associated with nonsuppurative encephalitis was reported in a captive killer whale

[104]. Additionally, health assessment seroepidemiologic studies of wild bottlenose dolphins in Florida demonstrated antibodies to several arboviruses including West Nile virus and Venezuelan, western and EEE viruses [103]. The combined data represent the first reports of these arbovirus pathogens in wild cetacean populations. The arboviruses examined in this study are commonly found in Florida, and the public health risks posed by these arboviruses are well documented [103, 105]. Evidence of exposure to these pathogens in the dolphin population may indicate mosquito transmission to dolphins from infected bird reservoirs in the same geographical regions as human case activity [103].

The flavivirus genus *Pegivirus* contains viruses that infect humans, nonhuman primates, bats, horses, rodents and pigs. Recently, the discovery of a near complete genome of a new species of pegivirus has been detected in wild bottlenose dolphins from the same health assessment study described above [8]. This novel dolphin pegivirus (DPgV) is thought to be the first member of the family Flaviviridae sequenced from a cetacean species and appears most closely related to porcine pegivirus and Theiler's disease-associated virus. Porcine pegivirus is associated with lameness and cutaneous vesicles in pigs while Theiler's disease is a common cause of acute hepatitis and liver failure in horses [106]. Interestingly, both cutaneous vesicles and acute hepatitis have been reported in the wild bottlenose dolphin population where DPgV was isolated, thus a causal relationship between DPgV and the previously reported pathologic findings cannot be ruled out [107, 108]. Further research is needed to evaluate the DPgV host range, zoonotic risk, route of transmission, prevalence and potential role in disease within wild and captive dolphin populations [8].

Herpesviruses

The number of marine mammal alpha and gamma HVs detected in the past 10 years has grown substantially and unique features of HV-associated disease such as viral latency are being further defined and elucidated [109, 110]. To this end, in-depth references and comprehensive reviews of marine mammal HVs can be found in Duignan *et al.* [46], Maness *et al.* [111] and van Beurden *et al.* [112]. A summary overview of characterized marine mammal HVs for which there appears to be an association with a clinical presentation or pathology is provided in Table 1. Most of the HVs identified in marine mammal tissues have been associated with relatively minor mucosal or epidermal lesions but are occasionally associated with fatal systemic or central nervous system infections in both pinnipeds and odontocetes [113–116].

Perhaps the most significant HV disease association is that between otarine HV-1 (OthV-1) and urogenital carcinoma (UGC) in California sea lions [130, 132]. UGC accounts for up to 18% of subadult and adult sea lion

mortalities for northern California with up to 26% of all animals in these age classes affected when non-fatal and microscopic lesions are factored in [133, 134]. OthV-1 is a gammaherpesvirus presently in an unclassified genus which is phylogenetically related to human HV 8 (HHV-8), an oncogenic HV associated with Kaposi's sarcoma [135]. Buckles *et al.* [131] showed that the virus was always present in tissue from sea lions with UGC and more common in tissues from the urogenital tract. An age-stratified study of prevalence among apparently healthy free-living sea lions found that 46% of adult males ($n=52$), 22% of adult females ($n=72$) but only 6% of juvenile sea lions ($n=120$) were OthV-1 positive by PCR. Furthermore, the virus was more commonly detected in swabs from the lower genital tract compared to swabs from the pharynx and peripheral blood leukocytes [132]. These results strongly suggested a sexual mode of transmission with similarities to the epidemiology of HHV-8 and Kaposi's sarcoma in people [136]. Studies are currently underway to determine whether known herpesviral oncogenes present in HHV-8 also occur in OthV-1 (Alissa Deming, personal communication, 2018).

Poxviruses

For more thorough reviews see Tryland *et al.* [137], Bossart *et al.* [40] and Van Bresse and Raga [138]. Cetacean and pinniped poxviruses are globally widespread and commonly found in regions where these marine mammal species are found. Cetacean poxvirus infections have been described in mysticetes and odontocetes including southern right whales (*Eubalaena australis*), humpback whale (*Megaptera novaeangliae*), bowhead whales (*Balaena mysticetus*), harbour and Burmeister's porpoises and bottlenose, striped, common, dusky (*Lagenorhynchus obscurus*) and Hector's dolphins (*Cephalorhynchus hectori*) [46, 76, 139–143].

Pinniped parapoxviruses are characterized in California sea lions, northern fur seals, harbour seals from the north Pacific ocean; ringed (*Pusa hispida*) and spotted seals (*Phoca largha*) from the Arctic; grey and harbour seals from the Atlantic; southern sea lions (*Otaria byronia*) from South America, Weddell seals from Antarctica; Mediterranean monk seals (*Monachus monachus*) and Baikal seals [137, 144–151]. A new species of poxvirus related to an orthopoxvirus was associated with raised, ulcerated cutaneous lesions in Steller sea lion (*Eumetopias jubatus*) pups [147, 152]. A novel poxvirus was also described in two orphaned northern and southern sea otters in California [153].

Poxviruses have been considered emerging pathogens in cetaceans and are presently classified into two major lineages: CePV-1 in odontocetes and CePV-2 in mysticetes [154]. Cetacean pox virus causes 'tattoo skin disease' (TSD) which is a poxvirus dermatopathy proposed to be caused by a new genus of *Cetaceanpoxvirus* most closely

Table 1 Herpesviruses of clinical significance in cetaceans and pinnipeds

Subfamily/genus	Host	Clinical significance	References
Alphaherpesvirus/Varicellovirus Phocid herpesvirus-1 (PhHV-1)	Harbour and grey seals	Pneumonia, adrenal and hepatic necrosis	111, 113, 115, 117
Delphinid herpesvirus-1 and 2 (DeHV-1 and -2)	Bottlenose dolphin	Multiple organ necrosis	111, 118
Delphinid herpesvirus-7 (DeHV-7)	Bottlenose dolphin (stranded)	Skin lesions	111, 119
Beluga whale herpesvirus-1 (BWHV-1)	Beluga whale	Genital ulcers	120
Alphaherpesviruses/Unclassified Delphinid herpesvirus (DeHV-3 and -8)	Bottlenose dolphin	Dermatitis	111, 121
<i>Stenella coeruleoalba</i> herpesvirus (Sc/2011/ENoAt Brain and Sc/2007/ENoAt Brain)	Striped dolphin	Encephalitis	122
<i>Stenella coeruleoalba</i> herpesvirus (Sc/2011/ENoAt Skin)	Striped dolphin	Dermatitis	199
<i>Ziphius cavirostris</i> herpes-virus (GU066291)	Cuvier's beaked whale	Lymphoid necrosis	123
<i>Mesoplodon densirostris</i> herpesvirus	Blainville's beaked whale	Nephritis	123
Harbour porpoise herpesvirus-2 (PPHV-2)	Harbour porpoise	Encephalitis	116
Gammaherpesvirus/Percavirus Phocid herpesvirus-2 (PhHV-2)	Harbour, hooded, ringed, harp seals, California sea lion	Possible neurological signs in hooded seals (no lesions reported)	111, 124, 125
Gammaherpesvirus/Macavirus PhHV-6	Harbour seals, northern elephant seals	Ocular swabs. Not associated with pathology	126
Gammaherpesvirus/Pinniped clade Otarine herpesvirus-3 (OthV-3)	California sea lion	Esophageal ulcers and B cell lymphoma	127
OthV-4	California sea lion	Ocular swabs. Not associated with lesions	126
PhHV-4	Northern elephant seal	Oral ulcers	111, 128
PhHV-7	Harbour and grey seals	Gingivitis or glossitis	83
Gammaherpesvirus/Toothwhavirus <i>Phocoena phocoena</i> or Phocoenid herpesvirus-1 (PPHV-1)	Harbour porpoise	Genital lesions	112, 116
<i>Kogia sima</i> herpesvirus-1 (KoHV-1)	Dwarf killer whale	Genital lesions	111, 112, 119
Delphinid herpesvirus (DeHV-6)	Risso's dolphin	Genital lesions	119
DeHV-4 and -5	Bottlenose dolphin	Genital lesions	111, 119
Ziphid herpesvirus-1 (ZiHV-1)	Blainville's beaked whale	Genital lesions	111, 129
Gammaherpesvirus/Unclassified OthV-1	California sea lion, South American fur seal	Neoplasia (urogenital carcinoma in California sea lions)	111, 130, 131

related to members of the *Orthopoxvirus* genus with different cetacean lineages [142, 147]. Grossly, TSD cutaneous lesions are typically randomly distributed, multifocal to coalescing, ring to pinhole shaped, flat, soft, black with a light grey margin and nonulcerative, ranging from 0.3 to 1 cm in diameter. Lesions occasionally have a black punctiform stippled pattern giving rise to the common name. Microscopically, the stratum externum of the lesions is moderately hyperplastic and ventrally compresses the underlying stratum intermedium. Keratinocytes of the stratum intermedium often have marked cytoplasmic vacuolation and contain variable numbers of spherical or irregularly shaped, pale, eosinophilic, intracytoplasmic

inclusions [40]. Ultrastructurally, the intracytoplasmic inclusions are composed of dumbbell-shaped virions [139]. Inflammation is not typically observed except in chronic cases that become secondarily infected with opportunistic organisms.

Cutaneous pox virus lesions of otarids and phocids are proliferative and characterized by hyperkeratosis and parakeratosis of the stratum spinosum and stratum corneum with often marked cytoplasmic vacuolation. Keratinocytes of the stratum spinosum may contain low variable numbers of spherical or irregularly shaped, pale, eosinophilic, intracytoplasmic viral inclusions [148]. A mixed inflammatory cell infiltrate also may be present.

In northern fur seals and South American sea lions, the nodular pox lesions are characterized by polygonal epithelial cells that proliferate into the dermis. These cells have abundant eosinophilic granular cytoplasm often with a single large round cytoplasmic inclusion body, a round vesicular nucleus and prominent nucleolus. Sea otter cutaneous pox lesions have epidermal hyperplasia with ulceration, and rete peg formation projecting into the dermis [153]. Intracytoplasmic inclusions consistent with Bollinger bodies may be present which ultrastructurally are consistent with pox inclusions.

Clinical and epidemiological data indicate that poxvirus infection in wild and managed odontocetes does not cause a high mortality rate when endemic [76, 77, 155, 156]. Stress, climate events, degraded environmental conditions and compromised general health appear to play a major role in the clinical manifestation of TSD [76, 77, 139, 141, 157, 158]. TSD in stranded Florida dolphins was speculated to be related to prolonged physiologic or pathologic stressors [107]. Additionally, TSD may be a general indicator of cetacean population health and the high prevalence of lesions in some adult odontocete populations may reflect immune suppression [40, 77, 108, 157]. Indeed, health assessment studies on free-living dolphins have documented immunologic perturbations with various infectious diseases which may further predispose susceptible individuals to TSD [6, 40]. Furthermore, dolphins from Florida health assessment studies are highly exposed to mercury, which also may be immunosuppressive [159–161]. This finding led to a recent study of mercury levels in coastal human residents, a seminal investigation which directly applied the findings from a sentinel species to identify a public health hazard in a contiguous human population [159]. Thus, environmental and anthropogenic factors were suggested to play a role in the pathogenesis, diversity and prevalence of TSD as well as other mucocutaneous lesions [6, 40, 160]. These studies illustrate and reaffirm the important role of dolphins as sentinels for marine ecosystem and public health.

Pinniped pox lesions demonstrate similar clinical and epidemiologic features to those seen in cetaceans. However, while cetacean pox viruses are species specific for odontocetes and mysticetes, pinniped parapoxviruses are zoonotic and can cause nodular painful proliferative cutaneous lesions in humans that are associated with fever and myalgia [162]. Thus, appropriate personal protective equipment and other precautions should be encouraged when working with stranded and wild pinnipeds.

Adenoviruses

Marine mammal adenoviruses belong to the genus *Mastadenovirus* and infect cetaceans, pinnipeds and otters [35, 98, 163–165]. Sea lion adenoviruses (OtAdV-1, OtAdV-2) were isolated from California sea lions while similar adenoviruses were found in liver samples or faeces

from pinnipeds including South African and South American fur seals, a South American sea lion and a Hawaiian monk seal [98, 166]. Adenoviruses have also been isolated from northern elephant seals (PhAdV-1), Pacific harbour seal (PhAdV-2), bottlenose dolphins (*Tursiops adenovirus-1*), sei whales (*Balaenoptera borealis*), bowhead whales, beluga whales, harbour porpoises and polar bears (*U. maritimus*) [98, 126, 164–173]. In otters, canine adenovirus-1 and a novel adenovirus have infected captive Eurasian otters (*Lutra lutra*) and southern sea otters, respectively [100, 174].

Lesions associated with adenovirus infection in pinnipeds include an acute necrotizing hepatitis, ulcerative keratitis, corneal oedema, iridocyclitis, arteritis and conjunctivitis with endothelial cell infection [46]. Eosinophilic intranuclear inclusions can be found in multiple tissues and endothelial cells. Ultrastructurally, adenoviruses-like virions are observed within the nucleus of affected hepatocytes and endothelial cells. No public health risk is known to exist at this time for people exposed to infected animals.

Coronaviruses

Coronaviruses (CoV) have been detected in captive and wild (alpha seal CoV) Pacific harbour seals, a captive beluga whale (gamma BWCoV) and captive Indo-Pacific bottlenose dolphins (*Tursiops aduncus*) (gamma BdCoV) [175–178]. Seal CoV is closely related to feline, canine, swine and ferret CoVs while the BWCoV and BdCoV are similar and have been proposed to represent a species specific cetacean CoV [176, 178].

Lesions identified in suspected coronavirus infection include an acute necrotizing enteritis and pulmonary oedema which was associated with acute death of three captive harbour seals [175]. Pulmonary congestion, haemorrhage and consolidation in five wild harbour seals with necrotizing lobar pneumonia and intralesional bacteria was reported in two of these seals from the same localized mortality event in central California [176]. Seal CoV was detected in lung tissue from this mortality event but a causal association could not be confirmed. The beluga whale referred to above had a severe centrilobular to coalescing hepatic necrosis. The bottlenose dolphins ($n=3$) had BdCoV detected in routine faecal samples and had no concurrent associated morbidity or mortality associated with CoV infection. Interestingly, BdCoV seroconversion was detected in these dolphins following BdCoV infection recovery [178]. No public health risk is known to exist in people exposed to CoV-infected marine mammals at this time.

Caliciviruses

Marine mammal viruses detected from the Caliciviridae family include the viruses in the Vesivirus, Norovirus and

Table 2 Other viruses of marine mammals

Virus	Characteristic	Host	Putative clinical association	References
Anellovirus (unclassified)	Non-enveloped, single-stranded (ss) DNA viruses	California sea lion, Pacific harbour seal, Southern sea otter, South American fur seal, Subantarctic fur seal	Associated with pneumonia in a California sea lion	100, 185, 186
Astrovirus (unclassified)	Non-enveloped, positive sense ss RNA viruses	Bottlenose dolphin, Steller sea lion, California sea lion, Minke whale	Unknown significance	183, 187
Picobirnaviruses	Non-enveloped double stranded (ds)-RNA virus	California sea lion, S. American fur seal	Unknown significance (enteritis in humans)	183, 186
Picornaviruses	Non-enveloped, positive-sense ss-RNA virus	Harbour and ringed seals, California sea lion, South American fur seal, Subantarctic fur seal	Phopivirus in livers of harbour seals that died from avian influenza H3N8. No hepatic pathology noted	183, 186, 188, 189
Rhabdovirus	Enveloped, negative-sense ss-RNA virus	Ringed seal, white-beaked dolphin, harbour porpoise	Rabies in ringed seal	190–192
Reovirus	Non-enveloped, ds-RNA viruses	Steller sea lion, South American fur seal, Subantarctic fur seal	Isolated from fetus and necrotic placenta of Steller sea lion	186, 193
Retrovirus	Enveloped RNA viruses	California sea lion, Killer whale, Southern sea otter	Alopecia in California sea lion	100, 124, 194
Asfarviruses	Enveloped, ds-DNA, arthropod-vector	California sea lion	Unknown significance	183
Circovirus	Non enveloped circular ss-DNA	New Zealand, South American and Subantarctic fur seals, Southern sea otter, Longman's beaked whale (<i>Indopacetus pacificus</i>)	Unknown significance	100, 171, 195, 196
Hepadnavirus	Enveloped, ds-DNA	Pacific white sided dolphin	Chronic active hepatitis, dermatitis	175
Parvoviruses	Non-enveloped, ss-DNA viruses	California sea lion, Southern sea otter, South American fur seal, Subantarctic fur seal	Unknown significance	100, 183, 186, 197, 198

Sapovirus genera [46]. The majority of the marine mammal vesiviruses are strains of vesicular exanthema of swine virus (VESV) and include San Miguel sea lion viruses SMSV-1 to SMSV-7, SMSV-9 to –11, SMSV-13 to- 17; Steller sea lion vesivirus SLVV-V810 and V1415; walrus calicivirus and cetacean calicivirus CCV-Tur-1. The pinniped vesiviruses SMSV-8 and SMSV-12 are genetically different from VESV and likely represent other vesivirus species [179]. Over 20 marine mammal vesivirus serotypes have been detected in Pacific marine mammals including California sea lions, northern fur seals, Hawaiian monk seals, Steller sea lions, Pacific walrus (*Odobenus rosmarus divergens*), bottlenose dolphins, grey whales (*Eschrichtius robustus*), fin whales, sei whales (*B. borealis*) and sperm whales (*P. macrocephalus*) [46, 180, 181]. Some serotypes can infect terrestrial mammals [46, 182].

Two sapoviruses (Csl SaV1 and Csl SaV2) were detected in faeces of California sea lions and closely related to SaV genogroup V and to the human SaV genogroup II, respectively. Noroviruses have been detected in the California sea lion and harbour porpoise which

are closely related to genogroup II norovirus and to a norovirus sequence detected in oysters, respectively [183, 184].

The consistent pathologic findings for marine mammal vesivirus infections are epidermal vesicles typically ranging from 1 to 3 cm which may coalesce and form bullae [46]. Vesicular and nonvesicular lesions also may involve mucocutaneous junctional tissue including the nasal mucosa. Viral replication in the stratum spinosum leads to vacuolar degeneration and necrosis which form focal intraepidermal vesicles. The vesicles eventually rupture often leaving shallow ulcers that typically heal uneventfully. VESV produces a disease in swine that is clinically indistinguishable from the viruses that cause foot-and-mouth disease and swine vesicular disease which gives VESV more historical significance than medical significance at this time. While not considered zoonotic viruses, care should be taken when working around marine mammal vesiviruses due to the wide range of species these viruses can infect. Additionally, the marine mammal sapoviruses and noroviruses have not been associated with

clinical signs or pathologic findings. However, porpoise norovirus has been shown to replicate in enterocytes [184]. This finding together with the genetic similarity between the porpoise norovirus and the oyster norovirus raises concern about significance of porpoise norovirus as a zoonotic pathogen.

Other Viruses

The list of other viruses that have been isolated or otherwise characterized from marine mammals continues to increase and are listed in Table 2. The clinicopathologic significance of many of these viruses remains to be determined.

Conclusions

As emerging viruses and associated diseases in marine mammals are being increasingly detected and characterized and the effects of ecologic and climate changes are becoming better appreciated, the health of the Earth's oceans has become a focus of intense public interest. One way of evaluating aquatic ecosystem health is developing and utilizing a sentinel species animal model. Such animal sentinels can provide critical advance notice of deleterious environmental health conditions and the potential related impacts on public and animal health associated with the oceans. Marine mammals are important sentinels for oceans and human health due to their many unique natural characteristics including their longevity, coastal habitation, high trophic level feeding and unique anatomic adaptations such as adipose tissue that can serve as depots for anthropogenic contaminants. Also, marine mammals are charismatic megafauna that typically elicit a notable human behavioural response. Consequently, many marine mammal species are now more likely to be considered deserving of our time and attention. The warning signs of possibly bigger and more complex marine mammal health problems associated with emerging diseases, particularly the viral diseases, remain a concern. This is particularly relevant since the emerging disease data suggest that complex interactions may occur among anthropogenic toxins, infectious agents and immunologic and genetic factors in many marine mammal species that live in a coastal environment with humans. Therefore, it is prudent for us to continue to characterize marine mammal health issues that could potentially impact our own well-being. The study of these complex disease issues presents opportunities to integrate the One Health approach of working collaboratively with members of multiple health professions. Global disease surveillance will require the collaboration and cooperation of physicians, veterinarians, epidemiologists, environmental biologists and others to detect and characterize emerging and novel viral diseases.

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