Personal View

Cetacean morbillivirus, a journey from land to sea and *viceversa*

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Abstract

Cetacean Morbillivirus, the most relevant pathogen impacting the health and conservation of cetaceans worldwide, has shown in recent years an increased tendency to cross “interspecies barriers”, thereby giving rise to disease and mortality outbreaks in free-ranging dolphins and whales. This "Personal View" deals with the evolutionary “trajectories” of this viral pathogen, likely originating from *Rinderpest Virus*, along with its "journey" from land to sea (and *viceversa*), mimicking that of cetaceans' terrestrial ancestors.

Cetacean Morbillivirus (CeMV), the most relevant pathogen impacting the health and conservation of several already threatened cetacean populations worldwide [1], has shown in recent years an increased tendency to cross “interspecies barriers” [2], thereby giving rise to disease and mortality outbreaks in free-ranging dolphins and whales [3-5]. Additional cases of infection have been also reported in aquatic mammals with a mixed aquatic-terrestrial ecology like common seals (*Phoca vitulina*) [6] and Eurasian otters (*Lutra lutra*) [7], with such findings increasing the overall concern and attention towards this *Morbillivirus* genus member. In this respect, the demonstrated ability of all the 5 hitherto chacterized CeMV strains to utilize indifferently dolphin, dog and seal SLAM/CD150 as host cell receptors [3] provides relevant biological plausibility and support to the aforementioned cross-species viral transmission events. Regarding its progressively expanding host spectrum range, CeMV shares similarities with *Canine Distemper Virus* (CDV), another global and multi-host morbilliviral pathogen responsible for numerous disease outbreaks in various terrestrial and aquatic wild mammal populations, including Lake Bajkal (*Pusa siberica*) and Caspian seals (*P. caspica*) [2, 8], which are known to be susceptible also to *Phocine Distemper Virus* (PDV) [9].

Based upon Bayesian phylogeographic analysis, CeMV has been estimated to be characterized by a mutational rate of 2.34×10^{-4} nucleotide substitutions/site/year, with viral evolutionary dynamics turning out to be neither host- nor location-restricted [3].

In this respect, it should be additionally highlighted that *Rinderpest Virus* (RPV), or a closely related ancestor of cattle origin, is believed to have crossed the "bovine-human transmission barrier" 1,000-5,000 thousands years ago, thereby giving rise to *Measles Virus*, the pathogen most closely related to RPV within the *Morbillivirus* genus [10]. The origins of rinderpest date back to over 10,000 years ago, coincident with cattle domestication in Asia [10], while the impact of RPV on cattle and on the human populations depending upon bovine productions has been so devastating throughout the centuries that rinderpest was the main motivation for establishing the first Veterinary School in Lyon, France, in 1761 [11]. In 2011, exactly 250 years later, the disease was declared to be globally eradicated, thanks to the use of an efficient anti-RPV vaccine [10, 11].

Due to the common terrestrial ancestor shared between cetaceans and ruminants [12], it could be speculated that the "land to sea transition" characterizing cetaceans' evolutionary phylogeny was probably followed also by CeMV, a marine virus most likely derived from RPV, a terrestrial pathogen [13, 14].

In this respect, while a CeMV isolate from the Southern Hemisphere that was identified almost simultaneously in Guyana dolphins (*Sotalia guianensis*) along the Atlantic coast of Brazil as well as in Indo-Pacific bottlenose dolphins (*Tursiops aduncus*) from Western Australia [15-17] appears to be the one most closely related to RPV among the 5 hitherto defined CeMV strains [3], it should be once again recalled that fatal cases of infection caused by *Dolphin Morbillivirus* (DMV, a CeMV strain) have been recently reported in Italy among Eurasian otters, an endangered wild mammal species with a mixed water-terrestrial ecology [7]. Furthermore, starting from 2011, DMV has shown a considerable expansion of its host range in the Western Mediterranean Sea, with lethal episodes of infection having been reported in fin whales as well as among mass-stranded sperm whales [4, 5, 18], while deadly cases of DMV infection have also been described in a Cuvier's beaked whale (*Ziphius cavirostris*) individual [19] and, surprisingly, even in a captive harbour seal [6].

Should this journey back from sea to land, putatively made by CeMV, worry us? And what implications, if any, could it exert on the feared RPV resurgence in cattle? In this respect, is there a concrete risk that rinderpest, the second infectious disease to be eradicated on Earth after smallpox [11], could re-emerge in cattle and should we pay attention, in such an undesirable *scenario,* to CeMV and its evolutionary dynamics?

Our answers to the above questions, based upon the so-called "principle of precaution", are affirmative.

As a matter of fact, a zoonotic potential has been recently documented for *Peste des Petits Ruminants Virus* (PPRV), another morbilliviral agent closely related to RPV, following a single amino acid change within its hemagglutinin (H) antigen [20]. Still notably, also CDV has been shown to successfully infect primate species phylogenetically close to humans, with reports of viral transmission to non-human primates under both natural and experimental conditions, together with a proven CDV adaptation to SLAM/CD150-expressing human cells following a single amino acid substitution in the viral H protein [21-23].

Finally and not less remarkably, it is our strong belief that adequate consideration should be also given to environmental radiocontamination as an additional factor potentially driving CeMV and, more in general, *Morbillivirus* and viral genetic make-up mutation(s). To the best of our knowledge, in fact, environmental radiocontamination has not received any attention within such complex and intriguing context. Nevertheless, it should be additionally underscored that, following the dramatic nuclear accident of April 1986 in Chernobyl, Ukraine, three major and entirely unprecedented morbilliviral disease epidemics took place in different aquatic mammal populations from European and neighbouring waters, namely among Lake Bajkal and North Sea common seals [9] as well as among Mediterranean striped dolphins (*Stenella coeruleoalba*) [1]. The three aforementioned outbreaks were respectively caused by CDV and by two newly discovered morbilliviruses, PDV and DMV [1, 9].

As a concluding remark, we believe that further work is absolutely needed in order to better characterize the transmission barrier(s) between CeMV and different cetacean, aquatic mammal and terrestrial hosts, along with the virus- and the host-related factors underlying cross-species jumping within aquatic and terrestrial environments as well as at the level of the various water-land ecological interfaces.

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