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Mapping the evolutionary trajectories of morbilliviruses: what, where and whither
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Morbilliviruses are pathogens of humans and other animals. Live attenuated morbillivirus vaccines have been used to end endemic transmission of measles virus (MV) in many parts of the developed world and to eradicate rinderpest virus. Entry is mediated by two different receptors which govern virus lymphotropism and epitheliotropism. Morbillivirus transmissibility is unparalleled and MV represents the most infectious human pathogen on earth. Their evolutionary origins remain obscure and their potential for adaption to new hosts is poorly understood. It has been suggested that MV could be eradicated. Therefore it is imperative to dissect barriers which restrict cross species infections. This is important as ecological studies identify novel morbilliviruses in a vast number of small mammals and carnivorous predators.

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What makes a morbillivirus?
At present six members of the Morbillivirus genus are recognized by ICTV (Figure 1). Measles virus (MV) is the prototype species and the others are Canine distemper virus (CDV), Rinderpest virus (RPV), Peste des petits ruminants virus (PPRV), Phocine distemper virus (PDV) and Cetacean morbillivirus (CeMV). When categorizing morbillivirus attributes it is essential to focus exclusively on wild-type morbillivirus strains as overarching generalizations cannot be made if vaccine viruses and laboratory-adapted strains are included since adaptation during in vitro passage in inappropriate cell lines is common. This is best illustrated by the first, and least clinically-relevant receptor identified for MV, CD46 [1,2] a cell surface molecule used in vitro by laboratory-adapted and vaccine strains but not by wild-type viruses [3]. Immunization of macaques with a recombinant (r) MV derived from the Edmonston-Zagreb (EZ) vaccine strain grown in CD46 expressing MRC-5 cells demonstrated that even though the vaccine virus uses CD46 in vitro this is not the case in vivo [4]. Following intramuscular injection only cells of the immune system were infected and the virus was not detected in neighboring muscle cells which express CD46. Therefore, for the purposes of generalization in this review we have selected six representative strains of known provenance, with confirmed virulence in natural hosts for which reliable full-length genomic sequences are available. These are the Khartoum Sudan (MV), Rhode Island US/2012 (CDVR1), Kabete ‘O’ Kenya/1910 (RPV), Wadden Sea NLD/1988 (PDV), Mediterranean Sea ESP/1990 (CeMV) and Côte d’Ivoire/1989 (PPRV) strains [5,6,7,8,9]. These are all characterized viruses used in many in vitro and in vivo studies, which are representative of other wild-type strains of known provenance and we simply use them to provide specific examples of key morbillivirus molecular signatures.

Genotypically, morbilliviruses are negative sense, non-segmented, single-stranded, RNA viruses, with genomes ranging from 15 690 to 16 050 nucleotides containing six transcription units (Figure 1). Full-length sequences have been obtained and although they share many common features seen in viruses from other Paramyxoviridae, Filoviridae, Bornaviridae and Rhabdoviridae families, they have several defining features. Morbillivirus genomes all conform to the ‘rule of six’ [10] meaning that the total genome length is divisible by 6 and have a large untranslated region located between the open reading frames encoding the matrix (M) protein and fusion (F) glycoprotein. The 3’ non-coding termini are 107 nucleotides in length and these contain the genome sense (CNS) motif at nucleotide positions 79, 85 and 91 [11], the corresponding position in the 17th hexamer (nucleotide 97) is also a conserved C nucleotide (Figure 1, red lines). These key molecular signatures, along with the presence of six transcription units, and a phospho- (P) protein gene containing an overlapping open reading frame encoding the non-structural C protein and an RNA editing site which leads to the incorporation of non-templated guanosine nucleotides into mRNAs which encode the non-structural V protein [12], are sufficient to recognize a genomic sequence as that of a
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Figure 1

Schematic representation of the genomic organization of known and proposed morbilliviruses. MV = measles virus (blue), CDV = canine distemper virus (red), RPV = rinderpest virus (green), PPRV = peste des petits ruminants virus (light orange), PDV = phocine distemper (dark orange), CeMV = cetacean morbilliviruses (yellow), FeMV = feline morbillivirus (purple) and DrMV = vampire bat morbillivirus (light blue). Genomes are drawn to relative scale for comparison of the 3' and 5' termini, open reading frames and intergenic sequence length. Open reading frames represent the nucleocapsid (N), phospho- (P), matrix (M), fusion (F), hemagglutinin (H) and large (L) proteins which are present in the virions. The P/V/C gene encodes the non-structural V and C proteins. Four conserved hexamers in the 107 nucleotide (nt) 3' leader sequence of MV are indicated (vertical red lines). The table lists known (gray) and proposed (white) morbilliviruses. Standard genome lengths, representative strains, proven CD150 and PVRL4 receptor use, 3' M gene untranslated region (UTR) lengths, the sequence of the non-transcribed intergenic (Ig) trinucleotide spacer between the M and F genes, the length of the 5' UTR of the F gene and available accession numbers on which the schematic diagrams, genome lengths etc. are based. Colors from this plate are used equivalently in figure 2 for clarity and comparability. * DrMV has not been isolated as a replicating virus.
morbillivirus. Interestingly these criteria were not applicable to ‘equine morbillivirus’ which emerged in Australia in 1994 [13]. Even though the genome organization is similar and the rule of six is obeyed the genome is considerably longer, the M/F untranslated region is much shorter, the 3′ non-coding terminus is 112 nucleotides long and there is an A nucleotide at position 97. Shortly after its discovery this previously unidentified zoonotic pathogen, which caused a fatal disease in people and horses, was renamed Hendra virus [14] and it is now a biosafety level (BSL)-4 agent grouped in the Henipavirus genus. This episode highlights the need to pay close attention to the genomic organization of emerging pathogens and judiciously select a name which ensures clarity. It also emphasizes the weaknesses of relying on small sequences from individual genes with a high level of conservation for taxonomic purposes.

Phenotypically, morbilliviruses share a number of biological features which also should be considered when novel viruses are discovered in clinical samples during ecological surveys. First and foremost, morbilliviruses are highly lymphotropic and CD150 (also known as signaling lymphocyte activation molecule/F1) is the universal receptor which is essential to initiate an infection [15**,16,17,18,19]. The molecule is present on the cell surface of subsets of T- and B-lymphocytes, dendritic cells and macrophages. Dendritic cells and macrophages in the respiratory tract have been identified as early target cells when MV is transmitted to a new host [6*,20]. In keeping with receptor mediated, host tropism human (h) MV uses hCD150 and bovine (b) RPV uses bCD150. This receptor is used by the vaccine virus in vivo even though CD46 can be used in vitro (see above). Although MV is first and foremost a human virus, species specificity is not exclusive, as illustrated by the fact that the wild-type readily infects marmoset (mar) B95a cells which express high levels of marCD150 [21]. Wildtype CDV uses canine (c) CD150 in vitro in Vero cells overexpressing the receptor although a change in the H glycoprotein is required for the virus to use marCD150 [22]. It could be argued that experimental confirmation of CD150-usage is non-negotiable prior to designating any closely related, novel virus as a morbillivirus. Poliovirus receptor-like 4 (PVRL4) is the second clinically-relevant morbillivirus receptor [23**,24,25**,26]. The HUGO Gene Nomenclature Committee is proposing to change the gene name to NECTIN4 (nectin cell adhesion molecule 4) since the current name does describe the function of adequately. Nectin-4/PVRL4 is present at the basolateral side of epithelial cells in the adherens junction and is critical in the later stages of the morbillivirus infections, being vital for transmission to susceptible hosts [27,28]. Significant levels of virus are present in the upper respiratory tract during the peak of infection and this contributes to the release of transmissible MV into the air [29]. Whether PVRL4/nectin-4 use should be considered as a defining characteristic of a morbillivirus in addition to CD150 use is open to question.

Where did morbilliviruses come from?

Due to the extreme transmissibility of morbilliviruses and the fact that infection leads to lifelong immunity, critical community sizes of 250 000–400 000 individuals are required to maintain endemic transmission [30]. It is likely that morbillivirus-infected ungulates were present in larger population densities earlier in history than humans leading to the assumption that RPV, or more probably an ancient precursor, predates MV [31]. What is certain is that in terms of the written historical record these are the two ‘oldest’ morbilliviruses. Rinderpest is thought to have originated in Asia (Figure 2a) long before cattle plagues were described in the Middle East, Africa and Europe in the first millennium BC. As such rinderpest can be considered as a disease of domestication. Although cities such as Rome and Alexandria had populations of around one million at the end of the 1st Century BC Hippocrates (ca. 460–370 BC) failed to list measles in his otherwise comprehensive categorization of childhood diseases including, for example, poliomyelitis and shigellosis [32]. The first written account of the disease is in a book by Muhammad ibn Zakariyā Rāzī, also known as Rhazes of Baghdad (ca. 850–932 AD). Based on thorough clinical descriptions Rāzī discriminated measles from smallpox as the ‘smaller disease’ hence ‘morbilli’, the diminutive of morbus [33]. Therefore even though measles is often referred to as a disease of civilization there is a disconnection between the development and growth of complex human societies from around 3000 BC to the definitive description of measles close to the end of the first millennium. These observations and genome sequence similarities have led to the suggestion that MV originated from an ancestral cattle virus which jumped species and RPV is the modern descendant of this ancient morbillivirus of ungulates (Figure 2a). Rinderpest was a devastating disease and mortality rates approach 100% in immunologically naïve herds [31,34]. It is reasonable to assume that some degree of adaptation to humans ensued after the first putative zoonotic transmission events and it is possible that initial mortality rates were higher in immunologically naïve populations. However, evolution could have increased person-to-person transmissibility and endemicity in the Old World would have driven the development of resistance in humans which in turn should decrease morbidity and mortality rates. Such post-zoonotic viral adaptation likely facilitates endemic diseases in established populations where person-to-person transmission is mediated by direct contact. Long established trade routes between the Mediterranean, the Indian subcontinent and the rest of Asia such as the Silk Road enabled both the transportation of cargo, and disease (Figure 2a). As new westerly trade routes opened to the New World in the 16th Century large, morbillivirus-naïve populations likely encountered well-adapted, highly transmissible viruses (Figure 2b). Much has been written about the origins and devastating effect of smallpox in the New World during the Age of Exploration [35]. Likewise the arrival of MV, an even more
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Figure 2

Representation of the approximate global distribution of morbilliviruses throughout history. (a) MV (blue) and RPV (green) are the oldest morbilliviruses which were spread along ancient trade routes (red arrows). (b) Importation of MV to the New World and CDV (red) to the Old World during the Age of Exploration. (c) Spread of RPV to Africa and Asia due to the trans-border movement of cattle and establishment of MV as the
transmissible pathogen was catastrophic and measles decimated thriving pre-Columbian populations in North, Central and South America and many Caribbean Islands, possibly by up to 95%. Mortality rates of 65% were reported as the disease spread rapidly and by the end of the 17th Century the virus was endemic in the New World. In 1657 Boston, Massachusetts experienced the first recorded outbreak in the 13 colonies and the disease seems to have been regularly reimported from Europe [36]. The city was the epicenter for frequent outbreaks and officials developed extensive contingency plans. For example, a ship arriving from Ireland in 1724 with measles patients was quarantined in Massachusetts Bay and an epidemic was avoided [36].

Dog distemper was first described in 1746 by Antonio de Ulloa y de la Torre-Giral (1716–1795 AD) following his travels in South America. Interestingly this is around the time a reciprocal, retrograde morbillivirus importation from the New to the Old World occurred as the ships which carried MV to the Americas brought CDV to Europe (Figure 2b). Mirroring the spread of measles in people in the Americas, CDV was reported first in Spain in the 1760s, described in England and Italy in 1764 and was present in Russia by 1770 [37*]. In 1809, Edward Jenner wrote ‘That disease among dogs which has familiarly been called ‘the distemper,’ has not hitherto, I believe, been much noticed by medical men’ and therefore he made a comprehensive description of the clinical signs and symptoms [38]. Jenner compared its transmissibility to measles, realized that puppies where particularly susceptible and recognized that survivors are protected from subsequent infection. Although the virus was recognized in dogs it infects many more species and is the most promiscuous of all known morbilliviruses, infecting ferrets, raccoons, tigers, lions, pandas and even primates [39,40,41,42]. This significant zoonotic potential makes CDV an ideal model to explore barriers which restrict cross species infections, for example dissecting the role of host-specific entry receptors and assessing the impact virus assembly in and virus egress from infected cells has on intra-host spread and inter-host transmission [22,43,44,45,46,47].

Over the following 250 years RPV, MV and CDV continued to expand their geographical ranges as new trade routes emerged and large scale transportation of livestock became possible due to the development of railroad networks. Rinderpest laid waste to massive numbers of cattle in Africa, India and Asia (Figure 2c) but the virus never made it to the New World. Measles killed significant proportions of Pacific Island dwellers and became the first verifiable global morbillivirus. However, even at the start of the 20th Century large numbers of adolescents had not been exposed to MV, demonstrating the importance of population movements and transportation in the global spread [48]. Distemper was identified as being caused by a filterable agent in 1905 by Henri Carte [49] and the English love of the domestic dog, particularly the foxhound, spurred the development of the first morbillivirus vaccine and introduced the ferret as a tractable small animal model for respiratory viruses [50**]. This in turn spawned the development of other morbillivirus vaccines in the middle of the 20th Century [51] (Figure 2c). Three new morbilliviruses were encountered, PPRV in 1942 [52], PDV in 1988 [53] and CeMV in 1991 [54] doubling the size of the genus (Figure 2c). Given the widespread distribution, multi-host infections and availability of many CDV isolates comprehensive phylogenetic relationships and nine genetic lineages have been described based on the sequence of the H gene [55]. Unsurprisingly these groups cluster geographically although their precise origins remain uncertain. Molecular phylogenetics has been used to examine how these historical clinical descriptions link to evolutionary predictions and the time to the most recent common ancestor (TMRCA) has been calculated as 1880 [56]. However, these calculations also suggest current CDV strains emerged from the United States, which is at variance with the description of the virus in Europe in the 18th Century. This highlights the challenges of modeling the evolutionary history of a virus with a highly labile RNA genome since many sequences are lost from the paleovirological record and questions have been raised about the utility of current TMRCA calculations [57]. A similar approach using whole genome sequences has been used to examine the molecular evolution of MV, RPV and PPRV [58]. This analysis suggests a TMRCA of 1904 (highest posterior density range 1730–1966) for PPRV strains and a TRMCA of 1666 (highest posterior density range 1072–1859) for MV/PPV/PPRV. An alternative molecular clock approach suggests 1074 (highest posterior density range 437–1576) as the date of divergence of RPV and MV [59]. No such analysis exists for PDV or the CeMVs although the course and outcome of the 1988 epizootic in seals suggests that this was a ‘virgin soil’ event [53]. Where the virus resides between outbreaks remains a

(Figure 2 Legend Continued) first globally distributed morbillivirus (MV and CDV are not indicated for the purposes of clarity). Discovery of PPRV (light orange), PDV (dark orange) and CeMVs (yellow) in small ruminants, seals and cetaceans respectively. Development of MV, RPV, CDV and PPRV live attenuated vaccines (v). (d) Discovery FeMV (purple) a proposed novel member of the genus in Asia and the United States. Determination of the sequence of DrMV (light blue with dashed line) from clinical material obtained in Brazil. PPRV expands geographical range in Asia and Africa and is commonly isolated in Turkey and China. Resurgence of MV (blue with red line) in regions of the world where endemic transmission had ceased via air travel, areas where MV is endemic are omitted for clarity. Detection of CeMV (yellow) in a broader range of more widely distributed marine mammals. Eradication of RPV and discontinuation of vaccine use in cattle. CDV remains globally distributed and is not indicated for the purposes of clarity.

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mystery and sequence analysis suggests a reintroduction event into seals in the North Sea [60,61]. It is likely these were spillover events and it is thus reasonable to propose the virus is maintained in other marine mammal species during the intervening period. For example interspecies transmission of CeCMV from a dolphin to a captive seal has been demonstrated [62]. Atlantic harp seal populations exceed 7 million which is well in excess of the numbers to maintain endemic transmission of a morbillivirus.

In the last 15 years there have been historic changes in morbillivirus global epidemiological patterns (Figure 2d). First, the use of a highly efficacious live attenuated vaccine has led to the eradication of rinderpest, with the last case diagnosed in Kenya in 2001 [63], and formal certification in 2011 by the Food and Agriculture Agency [64]. Second, vaccination led to the elimination of measles from the Americas in 2002, defined as the absence of endemic transmission in a specific geographic area for ≥12 months in the presence of a well-performing surveillance system [65]. There has been a consistent reduction in global mortality due to measles from 562,400 in 2001 to 122,000 in 2012 and it is estimated that vaccination prevented 13.8 million deaths. The impact of the Measles and Rubella Initiative has been significant, 215 million children were vaccinated in 2014 and ambitious goals have been set for the elimination of the virus in all other WHO regions (Measles and Rubella Initiative Annual Report). Third, PPRV has expanded both its geographical range and the hosts it infects. It has spread from goats to cattle [66], has been detected in camels [67] and the Asian lineage has spread to Africa [68]. It has been speculated that RPV eradication may be driving these changes as PPRV spreads eastward to China, northward to Turkey and southward throughout Africa [58]. However, increased surveillance cannot be excluded as a potential bias of the apparently higher PPRV incidence. Fourth, CeCMVs are now known to be globally distributed with viruses being isolated from dolphins in Australia and Brazil, and whales in Hawaii and the Canary Islands [53]. Fifth, CDV still circulates globally and has the potential to wreak havoc in endangered species, for example lethal infections have recently been diagnosed in Amur tigers making it a serious and emerging threat [69]. Outbreaks of CDV in China from 2006 [41] and Japan in 2008 [42] are particularly worrisome as this illustrates the potential for cross species jumps to primates. The implications of such a zoonotic infection occurring in a post-eradication MV-free world where vaccination during childhood has been discontinued could be catastrophic.

The recent description of several hundred viruses from small mammals which are phylogenetically related to the morbilliviruses, tentatively termed unclassified morbilli-related viruses (UMRV) has enabled new perspective on the origins of the genus. Most UMRV originate from bats (Figure 3), which is consistent with the prominent role of chiropteran hosts in paramyxovirus evolution and spread [70]. Detection of genetically closely related viruses in members of different mammalian orders is in keeping with a low degree of species specificity of at least some of these viruses [71]. The recent descriptions of feline paramyxoviruses clustering phylogenetically within the UMRV in an intermediate position between the genus Morbillivirus sensu strictu may hint at the acquisition of UMRVs by carnivore predators from small mammals. The relevance of small mammals and their carnivorous predators is consistent with their representation as morbillivirus hosts in the form of CDV, PDV and a partially characterized Brazilian vampire bat (Desmodus rotundus) morbillivirus (DrMV) [70]. The genetic diversity of UMRV outnumbers that of morbilliviruses many fold and it is tempting to speculate that all morbilliviruses have ancestral origins in small mammals. The ecological scenario of carnivores acquiring viruses from their prey is in line with the evolutionary origins of rabies virus in chiropteran hosts followed by an introduction into canids [72] and the acquisition of SARS-coronavirus by civets from bats [73]. Whether carnivores function as an entry point for viruses previously restricted to small mammals to infect a wider range of mammalian hosts is unclear. However, this is not without precedent as alteration of the SARS-CoV glycoprotein during passage in civets has been hypothesized [74] and rabies viruses acquired from insectivorous bats have established endemic circulation in several canids after the initial host switch [75]. Within the order Mononegavirales, the relevance of small mammal hosts in general and chiropteran hosts in particular, is demonstrated by the evolutionary origins of the closely related family Filoviridae in bats [76,77].

Whither morbilliviruses might go?
Knowing what morbilliviruses are, where they originated, how they have spread globally and that eradication is possible drives us to consider future evolutionary trajectories as new members of the genus are discovered and old members are eliminated. Successful eradication of RPV provides an impetus to eliminate MV and PPRV [64,78]. However, eradication of pathogens which have coexisted with humans and animals for thousands of years could also lead to unforeseen risks. Morbilliviruses are antigenically similar enough to permit dogs vaccinated with attenuated MV, to be protected from clinical signs of CDV following challenge [79,80]. Concerns have been raised that circulating morbilliviruses could spill over into naïve populations, for example by broadening their CD150 usage [39,78]. Adaptation studies to understand the likelihood of switches in viral tropism under accelerated evolutionary pressures would help address this issue. Even though RPV, PPRV and CDV infect multiple species there seems to be a significant barrier for these modern morbilliviruses to infect people and cause clinical disease. Clearly, CDV was present in South America before MV was imported from Europe and for whatever reason the virus failed to jump species to
Phylogenetic relationships of morbilliviruses and related small mammal viruses. Bayesian phylogenetic reconstruction done using MrBayes V3.1 with 2 000 000 tree iterations sampled every 100 steps, corresponding to 20 000 trees of which 25% were discarded as burn-in. The final tree was annotated using TreeAnnotator and visualized using FigTree from the BEAST package. Hendra virus was used as an outgroup. Host orders are indicated by color and pictograms to the right. Prototype morbilliviruses and related viruses are indicated next to branches (JPV, J virus; BeiPV, Beilong virus; TuPV, Tupaia paramyxovirus; see text for other abbreviations). All available unclassified morbilli-related viruses (UMRV) that differed by more than 5% in their partial L gene sequences from any other virus, were from different hosts or different sampling countries were included into the analysis. The final dataset comprised 205 partial L gene sequences of 438 nucleotides generated by the RT-PCR assay described by [83] commonly used in paramyxovirus field studies.

morbillivirus-naïve humans. Likewise PPRV causes subclinical infections of large ruminants in regions where RPV was eliminated and the virus failed to increase transmission or virulence. This indicates that CD150 use is not the only hurdle and intracellular factors are likely to play a significant role stopping cross species transmission events. This has been demonstrated experimentally by naturally infecting macaques with virulent CDV [45]. Although the virus infected many immune cells of the monkeys it was cleared rapidly and neurological signs were not observed. Why thousands of non-human primates succumbed to CDV infection in China [41] remains an enigma which needs to be addressed. A major challenge for MV eradication stems from resurgence of the virus in regions of the world where endemic transmission has been stopped (Figure 2d) due to the failure to use what is a safe and highly efficacious vaccine in some communities. Unsubstantiated links between the vaccine and a host of medical conditions alongside underestimation of the severity of the disease has led to large outbreaks in the developed world [81] with the inevitable concomitant measles-related deaths.
At the same time RPV was certified as eradicated another candidate morbillivirus was discovered [82]. Feline morbillivirus (FeMV) is present in urine and blood samples from domestic cats in Hong Kong (Figure 2d), full-length genome sequences have been reported in Japan [83,84] and we have shown it is present in the United States and causes a chronic infection [85]. However, if the criteria for ‘what makes a morbillivirus?’ are applied to FeMV only some are met, for example although the virus obeys the rule of six the M/F non-coding sequence is much smaller, there is an unusually long 3’ untranslated region in the L gene and importantly usage of feline CD150 has not been demonstrated. As noted above, FeMV clusters phylogenetically in basal sister relationship to classical morbilliviruses, exceeding the phylogenetic diversity within the genus. Lack of diversification within FeMV strains may suggest a limited evolutionary history within feline hosts after a putative host switch from small mammals.

A correlation with tubulointerstitial nephritis (TIN) has been suggested although Koch’s postulates have not been tested for FeMV in morbillivirus-naïve cats. CDV infects the bladder [86] and although throat swabs are the optimal specimen for detecting MV in clinical samples, the virus is also present in urine [87]. Acute renal failure concomitant with MV isolation in three patients with neurological complications has been reported although correlation does not equate to causation [88]. To date TIN has not been associated with any morbillivirus infection making the purported FeMV pathogenesis very different from the other viruses in the genus. Efforts should be made to address these important questions given TIN has a major impact on the quality of life of the 74–96 million domestic cats owned in the United States. This population size is more than sufficient to maintain endemic transmission of a morbillivirus even if lifelong immunity follows the acute infection. Whether this proposed morbillivirus makes it into the genus remains to be seen.

Ecological studies, degenerate reverse transcription PCR amplification and unbiased next generation sequencing approaches are being used to identify evolutionary ancestral viruses in a diversity of wildlife species from across the globe [70]. These approaches have radically altered our view of the number of potential viruses in the global ecosystem. However, given the challenges obtaining and storing clinical material, phylogenetic analyses often rely on short, highly conserved sequences which although useful for assessing the breadth and diversity tend not to be accompanied by biological isolates. Sampling tends to be focused on rodents and bats which could skew the phylogenetic analysis considerably and ideally the types of species examined should be expanded. Vampire bats sampled in Brazil [70] contained viruses which were very closely related to CDV and PDV (Figures 2 and 3). It is attractive to speculate that CDV and DrMV might share a common South American ancestor. However, in the absence of a DrMV vampire bat isolate and a complete genome sequence this hypothesis is challenging to test. Likewise, applying the ‘what makes a morbillivirus?’ test in terms of genome organization and receptor usage is not yet possible for DrMV. This highlights a major challenge in virus discovery, the gap between the identification of genomic fragments in clinical samples and understanding the biological properties of pathogens which could be impossible to isolate [89]. Synthetic biology offers an opportunity to bridge this gap and given the success with assembling reverse genetics systems for paramyxoviruses directly from unpassaged clinical material [90] it should be possible to develop completely synthetic reverse genetics systems as have been generated for non-segmented positive strand RNA viruses [91] and segmented negative strand RNA viruses [92]. For putative morbilliviruses such as DrMV this might be the only tractable option to obtain a cultivatable isolate. Piloting these technologies with a view to developing a pipeline to connect virus discovery and biological analyses will have a significant impact on understanding virus evolution and the propensity for cross-species jumps in the wild.

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