Temporal, geographic, and host distribution of *Avian paramyxovirus 1* (*Newcastle disease virus*)

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ABSTRACT

Newcastle disease is caused by virulent forms of avian paramyxovirus of serotype 1 (APMV-1) and has global economic importance. The disease reached panzootic proportions within two decades after first being identified in 1926 in the United Kingdom and Indonesia and still remains endemic in many countries across the world. Here we review information on the host, temporal, and geographic distribution of APMV-1 genetic diversity based on the evolutionary systematics of the complete coding region of the fusion gene. Strains of APMV-1 are phylogenetically separated into two classes (class I and class II) and further classified into genotypes based on genetic differences. Class I viruses are genetically less diverse, generally present in wild waterfowl, and are of low virulence. Class II viruses are genetically and phenotypically more diverse, frequently isolated from poultry with occasional spillovers into wild birds, and exhibit a wider range of virulence. Waterfowl, cormorants, and pigeons are natural reservoirs of all APMV-1 pathotypes, except viscerotropic velogenic viruses for which natural reservoirs have not been identified. Genotypes I and II within class II include isolates of high and low virulence, the latter often being used as vaccines. Viruses of genotypes III and IX that emerged decades ago are now isolated rarely, but may be found in domestic and wild birds in China. Containing only virulent viruses and responsible for the majority of recent outbreaks in poultry and wild birds, viruses from genotypes V, VI, and VII, are highly mobile and have been isolated on different continents. Conversely, virulent viruses of genotypes XI (Madagascar), XIII (mainly Southwest Asia), XVI (North America) and XIV, XVII and XVIII (Africa) appear to have a more limited geographic distribution and have been isolated predominantly from poultry.

Keywords

Avian paramyxovirus 1 (APMV-1), Newcastle disease virus (NDV), distribution, host, virulence, genotype

1. Introduction

1.1. Overview

Avian paramyxovirus 1 (APMV-1), synonymous with *Newcastle disease virus*, is a geographically widespread viral agent that infects wild, peridomestic (living in or around human habitations), and domestic avian hosts. For the purpose of the present review, the term APMV-1 will be used. Virulent strains of APMV-1 have significant global economic impacts on domestic poultry production and are notifiable to the World Organization for Animal Health (OIE). Additionally, virulent APMV-1 strains may negatively affect the caged bird trade and have implications for the management of wild birds (Bennejean, 1988). The importance of APMV-1 infections to avian health has long been recognized and therefore the subject of considerable scientific investigation. The incorporation of genetic data into APMV-1 research over the past several decades has greatly improved our collective inference of evolutionary based taxonomy of this viral agent as well as our understanding of temporal, geographic, and host ranges. Several classification systems for APMV-1 are available and have been used in the scientific literature, however discrepancies among the systems have made comparisons among studies challenging (Sakaguchi et al., 1989; Toyoda et al., 1989; Ballagi-Pordány et al., 1996; Aldous et al., 2003; Czeglédi et al., 2006; Diel et al., 2012a). As such, the goal of this review is to provide a summary of recent pertinent information, focusing on temporal, geographic, and host range of APMV-1 based on the most recent and objective nomenclature system (Diel et al., 2012a). A more in-depth analysis of the genetic diversity and classification of APMV-1 is in preparation by a consortium of international experts (Emmanuel Albina and Patti Miller, personal communication).

1.2. Viral agent and ecology

APMV-1 belongs to genus *Avulavirus*, family *Paramyxoviridae*, Order *Mononegavirales* (ICTV, 2012). Previously, APMV-1 was classified as member of genus *Rubulavirus* of the same order and the new genus *Avulavirus* was created in 2002 (Mayo, 2002a, 2002b). There are 9 accepted (APMV 1–9) (ICTV, 2012) and 4 putative serotypes (APMV 10–13) of APMV within the genus (Miller et al., 2010b; Briand et al., 2012; Terregino et al., 2013; Yamamoto et al., 2015). The nucleic acid of APMV-1 is single-stranded negative sense RNA (Alexander and Senne, 2008), has three genome sizes – 15,186 nucleotides (nt), 15,192 nt and 15,198 nt (Czeglédi et al., 2006) and codes for at least six gene products: the nucleoprotein (NP), phosphoprotein (P), matrix (M),

fusion (F), hemagglutinin-neuraminidase (HN), and the RNA polymerase (L) (Chambers et al., 1986). RNA editing of the P protein produces additional non-structural proteins V and possibly W (Miller et al., 2010a). The genomes of class II viruses of genotypes that are considered ‘‘historic’’ (i.e. I, II, III, IV) (1930–1960) consist of 15,186 nt, while viruses that emerged ‘‘later’’ (after 1960) (i.e. V, VI, VII, VIII, X-XVIII) contain 15,192 nucleotides. Class I APMV-1 genomes contain 15,198 nucleotides (Czeglédi et al., 2006; Miller et al., 2010a).

Virulent forms of APMV-1 cause Newcastle disease (ND), an economically important disease in poultry (Alexander and Senne, 2008). Additionally, APMV-1 strains of lower virulence have also been detected in numerous species of wild birds which may or may not result in clinical disease (e.g., Rosenberger et al., 1974; Kaleta and Baldauf, 1988; Wobeser et al., 1993). Although some viruses may be differentially maintained in wild or domestic bird reservoirs, there is also evidence for viral transmission across the poultry-wild bird interface (Kim et al., 2007a; Cardenas Garcia et al., 2013). APMV-1 is transmitted through either inhalation or ingestion (Alexander et al., 1984; Li et al., 2009; Miller and Koch, 2013) and can remain infective for long periods of time given proper environmental conditions (Davis-Fields et al., 2014). Therefore, multiple potential routes of transmission and the ability of the viral agent to persist in the environment may facilitate interspecies transmission and the potential for spread across domestic-peridomestic-wild bird interfaces.

1.3. Pathogenicity

Several pathogenicity tests have been developed to determine the pathogenicity of APMV-1 strains in chickens (Miller and Koch, 2013) and the intracerebral pathogenicity index (ICPI) is the current *in vivo* standard for the OIE (2012). APMV-1 strains produce a range of pathogenic outcomes in poultry. Viruses of low pathogenicity, or lentogens (ICPI $\leq$ 0.7), generally result in subclinical disease whereas those of moderate pathogenicity, or mesogens (ICPI > 0.7 but $\leq$ 1.5), generally cause clinical signs of disease, but typically result in non-lethal outcomes in chickens. Viruses of high pathogenicity, or velogens (ICPI > 1.5), cause serious disease and mortality among affected birds. Clinical signs of infection with APMV-1 may include: decreased egg production, depression, diarrhea, respiratory distress, neurologic signs, torticollis, and death.

A wide range of pathogenicity for APMV-1 strains is also found in wild birds. Lentogenic viruses are relatively common in wild waterfowl, gulls, and shorebirds and apparently do not cause clinical disease (e.g., Rosenberger et al., 1974; Kim et al., 2007b; Ramey et al. 2013). In contrast, mesogenic/velogenic viruses have caused recurrent outbreaks of disease in pigeons and double-crested cormorants (*Phalacrocorax auritus*) in the mid-continent of North America (Wobeser et al., 1993; Banerjee et al., 1994; Kuiken et al., 1998; Glaser et al., 1999; Kim et al., 2008; Rue et al., 2010; Diel et al., 2012b). The strains from pigeons are antigenic variants of APMV-1 and are often referred to as pigeon paramyxovirus 1 or PPMV-1. Mortality in wild birds attributed to ND has occurred exclusively among young, hatch-year cormorants (Kuiken 1999). Highly virulent viruses have also been isolated in psittacines in quarantine stations and in a variety of wild bird species in zoos and live bird markets; however, it is not clear if these viruses represent spillover events from poultry or if viruses are maintained in wild and pet birds (Senne et al., 1983; Panigrahy et al., 1993; Alexander et al., 2011; Vidanovic et al., 2011; Snoeck et al., 2013b; Byarugaba et al., 2014; Mulisa et al., 2014).

Virulence is primarily a function of the fusion gene (Nagai et al., 1976), which has resulted in considerable scientific investigation focused on this gene product; but all other genes likely play important roles in modulating the capacity of the virus to replicate and cause disease (Dortmans et al., 2011). Genetic analyses have revealed the nucleotide sequence of the cleavage site of the fusion gene to be predictive of potential pathogenicity of APMV-1 strains (Glickman et al., 1988; Collins et al. 1993). Virulent APMV-1 strains have three or more basic amino acids (arginine or lysine) at positions 113 to 116, and a phenylalanine at position 117 at the fusion protein cleavage site, whereas APMV-1 strains predicted to be of low virulence have fewer than two basic deduced amino acid residues at the fusion cleavage site, with a leucine at position 117 (Glickman et al., 1988). As such, predicted virulence based upon deduced amino acid motifs at the fusion cleavage site has been incorporated into the definition of notifiable APMV-1 strains by the OIE (2012). Although there are not many documented cases, there is evidence that APMV-1 of low virulence may evolve into a virulent phenotypes as few point mutations are sufficient to result in the emergence of virulent forms of APMV-1 (Collins et al., 1998; Gould et al., 2001; Miller et al., 2010a; Alexander, 2011)

2. Genetic diversity, classification and distribution

Genetic analysis of nucleotide sequences for the complete coding region of the fusion gene has recently been proposed as the basis for a unified nomenclature and classification system for assigning APMV-1 isolates into evolutionary related groups (Diel et al., 2012a). Based upon previous analyses of AMPV-1 genomes (Czeglédi et al., 2006) and criteria incorporated into this recent classification system, there are currently two genetically divergent 'classes' of APMV-1. Class I isolates belong to a single 'genotype' whereas class II isolates are divided into 18 genotypes (Diel et al., 2012a; de Almeida et al., 2013; Courtney et al., 2013; Snoeck et al., 2013c; Susta et al., 2014b) (Figure 1; Table 1). The Diel et al. (2012a) classification system attempts to maintain previously classified genotypes and also incorporates objective genetic criteria for classification. A 10% mean nucleotide difference of the fusion protein gene coding sequence is required to assign phylogenetically distinct groups of viruses into genotypes. Additionally, at least four epidemiologically independant isolates have to form a distinct taxonomic group in a phylogenetic tree with a bootstrap value at the defining node > 60 to designate a unique genotype. Exceptions were made for genotypes III, IV and IX, which present slightly lower mean genetic distances among genotypes (Table 1, shaded). These exceptions were established by Diel et al. (2012a) in order to maintain the classification commonly used throughout existing literature. Some genotypes are further divided into 'sub-genotypes' based upon calculations of intra-genotype genetic diversity (Diel et al., 2012a). The mean genetic distance per site in the range of 3–10% and a bootstrap value > 60 at a defining node are used as cutoff values for assigning new sub-genotypes.

Based on the complete coding sequence of the fusion protein gene, the viruses of class I are 54.4–62.8% genetically divergent from the class II genotypes viruses with 59.5% overall distance between these two major groups. Class I viruses are less diverse among themselves with 5.9% differences between all known isolates. Class II viruses are more diverse (Table 1) with nucleotide distances between genotypes varying from 7.8–28.9% at the fusion gene. The largest genetic distance is observed between genotypes XI and XIV (28.9%) and between 12.8–26.6% when compared to the rest of the genotypes. Viruses of these two genotypes have been isolated in only limited geographic areas – Madagascar (XI) and Nigeria, Benin and Mali (XIV) during the last 10 years. Additionally, the genetic distance between the "historic" genotypes (I, II, III, IV and IX) is ≤14.4% while the distance between these genotypes and those more recently identified (XIII, XIV, XV, XVI, XVII and XVIII) is higher (15.9–26.6%).

In the following sections, we review viral pathogenicity and temporal, geographic, and host range of viruses for each APMV-1 genotype based upon this latest classification system that utilizes the complete coding region of the fusion gene. For this purpose we have created and curated a database populated with all complete fusion gene sequences for APMV-1 (n=1299) available in the GenBank database (Benson et al., 2015) as of 29 August 2015 (Supplemental Table S1) and temporal, host and geographic information available for these isolates. For the purpose of this review, Benson et al. (2015) will be also used to refer to sequences that have been submitted to GenBank but do not have citations in peer reviewed journals. In addition, to increase the utility of this review by facilitating comparisons to previously published literature, we have included selected genotype information based on the partial fusion gene of APMV-1 isolates (e.g., the 374 base pair fragment commonly amplified in previous studies) for genotypes and sub-genotype that may be underrepresented in our dataset (e.g., genotypes III, IV, V and sub-genotypes VIb, Vid, VIIa and VIIc). Because sampling efforts for APMV-1 have been biased toward poultry and hosts that are specific for avian influenza, it is possible that there is still undetected diversity of virulent and non-virulent viruses in free-ranging avian species. However, despite these limitations, it is our hope that this review will be useful for compiling information derived from a large number of scientific investigations conducted across the globe on APMV-1 into a unified and intelligible context.

2.1. Class I

APMV-1 class I isolates share sufficient genetic similarity to be considered a single genotype (genotype 1). Viruses of class I genotype 1 are currently divided into three sub-genotypes: 1a, 1b and 1c. There is a possibility that additional class I sub-genotypes exist as there are two clearly distinct groups of viruses that meet the genetic distance criterion but lack the necessary number of epidemiologically independent isolates (Diel et al., 2012a). Class I isolates have been recovered from both domestic and wild birds sampled in North America and Eurasia since at least 1987 (Kim et al., 2007b). Recent isolations suggest that class I viruses continue to infect birds in the United States (Pedersen et al., 2014) and China (Fan et al., 2015).

Viruses of class I genotype 1 sub-genotype 1a have been repeatedly recovered from domestic ducks (*Anatidae spp.*), chickens (*Gallus gallus domesticus*) and geese in China during 2007–2010 (Liu et al., 2009; Benson et al., 2015). The temporal, geographic, and host

distributions of sub-genotype 1b viruses are similar to those of viruses in sub-genotype 1a. Viruses of sub-genotype 1b have been identified in variety of birds including chickens, ducks, black swan, peafowl, egret and heron in China during 2009–2013 (Fan et al., 2015; Benson et al., 2015).

Class I sub-genotype 1c viruses have primarily been recovered from ducks, swans, geese, and shorebirds in the United States since 1998 (Kim et al., 2007b; Ramey et al., 2013; Pedersen et al., 2014) with closely related viruses also having been isolated from domestic poultry at live bird markets (Seal et al., 2005; Kim et al., 2007b). Additionally, sub-genotype 1c isolates have been recovered in Europe (1999–2010) and Asia from a variety of wild waterbirds including ducks and gulls (Lindh et al., 2012; Ramey et al., 2013), as well as from domestic ducks, particularly in China (Liu et al. 2009; Meng et al., 2012).

All but one strain of class I APMV-1 viruses are considered to be of low virulence in chickens as based upon deduced amino acid motifs at the fusion cleavage site (Glickman et al., 1988) and pathotyping of representative viruses (Liu et al., 2009). Notably, in 1990 a ND outbreak caused by a class I virus of high virulence was recorded in Ireland (Alexander et al., 1992). It has been subsequently demonstrated that only a few point mutations were required to develop a virulent virus from the APMV-1 of low virulence that was circulating in waterfowl in the same area as the ND outbreak in poultry (Collins et al., 1998).

2.2. Class II genotype I

APMV-1 class II genotype I isolates are currently classified into three sub-genotypes: Ia, Ib, and Ic. Viruses of sub-genotype Ia include velogenic strains recovered from chickens in Australia during 1998–2002 (Gould et al., 2001; Kattenbelt et al., 2006; Susta et al., 2011) and strains of low virulence isolated from wild waterfowl and poultry samples collected in China, Colombia, Malaysia, and South Korea during 1998–2014 (Kim et al. 2012; Diel et al., 2012a; Benson et al., 2015). The Queensland V-4 vaccine strain is also classified within sub-genotype Ia. Phylogenetic analysis of sub-genotype Ia isolates provides support for the existence of an exchange of viruses between wild birds and domestic poultry, and potential vaccine escape (Kim et al. 2012).

Class II genotype I sub-genotype Ib isolates have been recovered from a diversity of wild and domestic waterfowl in China, Japan, Luxembourg, Madagascar, Nigeria, Russia, South

Korea, Ukraine, and the United States (Liu et al., 2009; Kim et al. 2012; de Almeida et al., 2013, Ramey et al., 2013; Snoeck et al., 2013a; 2013b; Muzyka et al. 2014) during 2001–2011. Deduced amino acid motifs at the fusion cleavage site and ICPI values for viruses of this sub-genotype suggest that all isolates recovered to date are lentogenic. Phylogenetic analyses suggest that wild birds may play a role in the dispersal of viruses of this sub-genotype within and among continents (Ramey et al., 2013; Muzyka et al. 2014). The extensively studied strain, Ulster/chicken/Ireland/1967, is also included in this sub-genotype.

Sub-genotype Ic isolates have been recovered from shorebirds, waterfowl, gulls, and various landbirds sampled in Japan, Mexico, Russia, Sweden, and the United States (Kim et al., 2007b; Munir et al., 2010; Cardenas Garcia et al., 2013; Ramey et al., 2013) during 1994–2009. Similar to sub-genotype Ib, these viruses have all been predicted to be lentogens and may be maintained and intercontinentally dispersed by wild birds (Kim et al., 2007b; Ramey et al., 2013).

2.3. Class II genotype II

Class II genotype II isolates were first reported in North America and have been also identified in Africa, Asia, Europe, and South America, primarily in gallinaceous poultry and domestic waterfowl (Seal, 2004; Snoeck et al. 2013c; Uthrakumar et al., 2014; Benson et al., 2015). Viruses of this genotype are also the constituents of most widely used ND live and inactivated vaccines (e.g. LaSota and B1). There have also been a few detections of class II genotype II viruses in peridomestic and wild birds suggesting potential spillover into free-ranging hosts (Zanetti et al., 2005; Zhu et al., 2010; Cardenas Garcia et al. 2013; Yuan et al., 2013). Many class II genotype II isolates have been pathotyped as velogens or are predicted to be virulent (Seal, 2004; Mohamed et al., 2011; Uthrakumar et al., 2014), which adds to the economic importance of viruses of this genotype to poultry production. Many isolates recovered from poultry are likely the result of introductions of live vaccine viruses (e.g., the widely used class II genotype II LaSota vaccine strain) into poultry production systems through vaccination efforts (de Leeuw and Peeters, 1999; Khan et al., 2010; Benson et al., 2015). Complete fusion gene sequences are available for class II genotype II strains isolated in the United States and Italy from as early as the 1940s (Toyoda et al., 1989; Seal, 2004) and viruses of this genotype may continue to circulate among poultry in many regions of the world (Benson et al., 2015).

2.4. Class II genotype III

Based on the partial fusion gene sequences, viruses of class II genotype III have been isolated primarily form Southeast Asia (Ballagi-Pordány et al., 1996; Aldous et al., 2003). "Ancient" isolates from Australia in 1932 and Japan during 1930–1960 are described as members of this genetic group (Ballagi-Pordány et al., 1996; Lomniczi et al., 1998). Viruses of the same genotype have been also sporadically isolated in UK, Taiwan, Zimbabwe, and Singapore during the 1960s and early 1990s. Only a limited number of complete fusion sequences is available for viruses of class II genotype III. All viruses of this genotype are virulent based on the predicted amino acid sequence at the cleavage site of the fusion protein. Class II genotype III isolates have been recovered from chickens in Pakistan in 1974 and, more recently, chickens and domestic waterfowl in China during 2000–2005 (Tang et al., 2005; Zhang et al., 2008; Qiu et al., 2009; Khan et al., 2010). There is evidence suggesting that the emergence of recent class II genotype III viruses may have resulted from the escape and subsequent mutation of the vaccine strain Mukteswar/chicken/India/1940 (Aldous et al., 2003; Qiu et al., 2009). This strain has been pathotyped as mesogenic (Czeglédi et al., 2003), laboratory-attenuated after passages in eggs, and subsequently used widely as vaccine, primarily in Southeast Asia (Aldous et al., 2003).

2.5. Class II genotype IV

APMV-1 class II genotype IV viruses include isolates recovered from poultry in Europe during 1933–1944 (de Leeuw et al., 2005; Wei et al., 2008) and are considered to be the predominant viruses isolated in Europe before 1970 (Ballagi-Pordány et al., 1996; Czeglédi et al., 2006). Additionally, isolates of this group have been also recovered from poultry in Africa (Sudan) in 1991, pigeons in Asia (Hong Kong) in 1989 and poultry in Russia in 1970 (Aldous et al., 2003; Miller et al., 2010). These viruses are considered virulent and include the well-characterized Herts/33 virus which may not have actually originated in Hertfordshire, England in 1933 (Czeglédi et al., 2003). Rather, this virulent strain may have been isolated elsewhere in Europe in the 1940s (Czeglédi et al., 2003). Since the designation Herts/33 has been used for this representative of class II genotype IV virus for many years (Wehmann et al., 2003; Kim et al., 2007a; Diel et al., 2012;) we have also used it for the purpose of this review. Given the lack of

genetic information for contemporary genotype IV isolates, it is plausible that these viruses are no longer maintained in poultry.

2.6. Class II genotype V

Class II genotype V viruses likely emerged in Central and/or South America in 1970s and subsequently introduced into Europe (Ballagi-Pordány et al., 1996; Miller et al., 2010). It has been reported that these viruses spread very fast due to their association with psittacine species and the global trade of these birds (Ballagi-Pordány et al., 1996). Based on partial fusion gene sequences it has been shown that after the first appearance of genotype V viruses into Europe, they spread throughout the whole continent affecting poultry during 1970s and 1980s (Ballagi-Pordány et al., 1996; Lomniczi et al., 1998; Czeglédi et al., 2002). Viruses form this genotype have also been recovered from poultry and ducks in East and West Africa (Ballagi-Pordány et al., 1996; Aldous et al., 2003). Viruses of class II genotype V are all predicted to be virulent based on genetic sequencing although many strains are mesogenic via pathotyping. Based on complete fusion coding sequences viruses of class II genotype V are currently divided into four sub-genotypes: Va, Vb, Vc and Vd.

Sub-genotype Va viruses have been recovered since 1995 almost exclusively from wild birds sampled in the United States and Canada (Miller et al., 2009; Rue et al. 2010; Diel et al., 2012b), with exceptions being a detection of a sub-genotype Va virus in a North Dakota free range turkey farm in 1992 and a cormorant in Minnesota during the same year. Sub-genotype Va viruses have been associated with recurrent outbreaks of disease in double-crested cormorants in North America (Rue et al. 2010; Diel et al., 2012b). Additional isolates have been recovered from samples taken from pelicans and gulls in close proximity to cormorants during outbreaks (Heckert et al., 1996; Diel et al., 2012b) and these isolations may be indicative of spillover events among wild birds. The detection of sub-genotype Va viruses in cormorants in Michigan, Minnesota, and North Dakota during 1992 (Benson et al., 2015) and relatively close phylogenetic relationship with those isolates recovered from a turkey farm, provide further evidence for the transmission of APMV-1 across the wild bird-poultry interface.

Virulent sub-genotype Vb viruses have been recovered from a variety of poultry, caged-birds, and peridomestic species in the United States, Brazil, Central America, and Africa since the 1970s (Pedersen et al. 2004; Fernandes et al., 2014; Susta et al. 2014a; Wise et al., 2004).

There is some evidence for spill-over of viruses of this sub-genotype into free-living birds in Mexico (Cardenas Garcia et al., 2013), yet there is no evidence of expansion of this group into other continents. Evolution of sub-genotype Vb has been found to occur within the Neotropics (Susta et al. 2014a). APMV-1 class II genotype V sub-genotype Vc viruses are similar to those of sub-genotype Vb in that they have been circulating in Mexico and Central America mainly in poultry but also in caged-birds, tree-ducks and quail. Recently classified class II sub-genotype Vd includes viruses isolated from poultry in Kenya and Uganda during 2010–2011, but there is evidence that these viruses circulated in Uganda as early as 2001 (Byarugaba et al., 2014).

2.7. Class II genotype VI

Viruses in class II genotype VI, sometimes referred to as pigeon paramyxovirus serotype 1 or PPMV-1, are considered to be panzootic yet somewhat limited in host range. Viruses of APMV-1 class II genotype VI are highly diverse genetically and currently divided into nine sub-genotypes: VIa–VIi. Similar to genotype V, all viruses within class II genotype VI are predicted to be virulent in poultry with deduced amino acid motifs suggestive of high pathogenicity; however, most strains may be phenotypically mesogenic as assessed through ICPI testing (Dortmans et al., 2010). Detections of most sub-genotypes of class II genotype VI viruses have occurred primarily in birds of the family *Columbidae*, which includes numerous species of wild and domestic pigeons and doves, while a few others have been detected more frequently in poultry. Viruses of this genotype have likely spread geographically through both the trade of racing pigeons as well as through dispersal by free-ranging pigeons and doves (Kaleta et al., 1985; Alexander, 2011).

Class II genotype VI sub-genotype VIa viruses have been reported almost exclusively in Columbidae birds at locations in Asia, Europe, the Middle East, and the United States since the 1990s (Kim et al., 2008; Guo et al., 2013; Snoeck et al., 2013b; Benson et al., 2015) with infrequent reports from poultry likely to be spillover from reservoir hosts. Similarly, full fusion gene sequences for sub-genotype VIb viruses have been reported primarily in pigeons in Argentina, China, Italy, and the United States during 1984–2007 (Ujvari, 2006; Miller et al., 2007; Benson et al., 2015) with an exception being the recovery of sub-genotype VIb viruses from poultry in Great Britain (Alexander et al., 1999). A series of investigations provided

evidence that poultry feed contaminated by infected pigeons has led to numerous outbreaks of disease in unvaccinated chickens (Alexander et al., 1984; Alexander et al., 1985; Aldous et al., 2004; Alexander et al., 2011). As inferred from the partial fusion gene sequences, the first identified viruses of class II sub-genotype VIb originate from the Middle East during the late 1960s and early 1970s (Lomniczi et al., 1998; Czeglédi et al., 2002). Isolates of sub-genotype VIb have been also recovered predominantly from pigeons (but also kestrels, falcons, cockatoos, budgerigars, pheasants, swans and a robin) in Europe, South Africa, and the Far East since 1970s (Abolnik et al., 2008). Viruses of this sub-genotype are still circulating and have been identified in Europe since the beginning of the 21st century (Alexander, 2011).

Full fusion sequences for sub-genotype VIc viruses have been reported for isolates recovered in chickens in East Asia in the 1980s and 1990s (Liu et al., 2003; Umali et al., 2014). It is unclear if these viruses have shared ancestry with predecessor strains to panzootic viruses in *Columbidae* birds or whether they represent spill-over of strains circulating in *Columbidae* birds and subsequent viral evolution within domestic poultry. Sub-genotype VId was previously identified based on the 374 base pair region of the fusion protein gene and comprised isolates from poultry in Europe during the 1990s (Lomniczi et al., 1998). Unfortunately, there is currently a lack of sequence information for the full fusion gene of such isolates and therefore this sub-genotype currently is unpopulated based on the unified nomenclature system. The lack of complete fusion gene sequence information for representative viruses from APMV-1 class II genotype VI sub-genotype VId represents a gap in the evolutionary record of this viral agent.

Viruses from sub-genotype VIe–VIi have been recovered from primarily *Columbidae* birds at numerous locations throughout world; however, there may be differences in geographic distribution of isolates. Sub-genotype VIe viruses have been recovered from pigeons, and apparently less frequently in poultry, in China during 1996–2012 (Liu et al., 2003; Benson et al., 2015). Sub-genotype VIf viruses have been repeatedly recovered from pigeons in the United States during 1984–2007 (Hines et al., 2012; Benson et al., 2015). Viruses from sub-genotype VIg have been isolated from pigeons and a dove in Nigeria, Russia, and Ukraine during 2005–2011 (Van Borm et al., 2012; Pchelkina et al., 2013; Yurchenko et al., 2015; Benson et al., 2015). The earliest confirmed subtype VIh isolate was recovered from a pigeon in Argentina in 1997 (Benson et al., 2015), but subsequent reports of viruses of this subtype have originated from pigeons and doves in Kenya and Nigeria during 2007–2013 (Van Borm et al., 2012; Snoeck

2013a; Benson et al., 2015). Relatively few isolates of sub-genotype VIi have been genetically characterized and they have been recovered from collared doves (*Streptoelia decaocto*) in Italy in 2010–2011 (Bonfonte et al., 2012) and pigeons in Nigeria in 2013 (Snoeck 2013a).

There is a group of viruses that has only been found in chickens in Ethiopia (during 2011-2012) (de Almeida et al., 2013; Mulisa et al., 2014) and is highly related to viruses of genotype VI. It is possible that viruses of this group emerged in Africa after the introduction of ancestral class II genotype VI viruses from Columbidae birds into poultry (Mulisa et al., 2014) and that low biosecurity and trade practices in Ethiopia may have facilitated the establishment and spread of these viruses in poultry in this region (Mulisa et al., 2014). This group of viruses fulfils the criteria set by Diel et al. (2012a) and may represent a new sub-genotype within genotype VI that is yet to be designated.

Within class II genotype VI there are inconsistencies regarding taxonomic classification in the literature. For example, de Almeida et al. (2013) designated the viruses from the United States isolated between 1984–2007 and described above as sub-genotype VIf (as consistent with Snoeck et al., 2013) as sub-genotype VIh. Furthermore, the authors suggest that viruses isolated from samples collected in Ethiopia during 2011–2012 should be designated as sub-genotype VIf. The same authors also propose a group of viruses containing only isolates from the United States, previously classified as members of sub-genotype VIa, to be separated in sub-genotype VIi (different from the sub-genotype VIi described in the previous paragraph). Such differences in APMV-1 classification are subject to re-classification by a large group of international experts working on uniform system for defining sub/genotypes of this viral pathogen (Emmanuel Albina and Patti Miller, personal communication).

2.8. Class II genotype VII

Genotype VII is another large and genetically diverse group of viruses. Class II genotype VII viruses likely emerged in the Far East in the 1990s and subsequently spread to Asia, Europe, South Africa and South America. Viruses of this genotype are currently divided into sub-genotypes VIIa–VIIi, although some sub-genotypes (i.e., VIIa and VIIc) that were previously assigned using only the limited genetic information of the partial fusion gene remain unrepresented with regard to complete fusion gene sequences. All genotype VII viruses are predicted to be virulent based on deduced amino acid motifs and many have been shown to be

velogenic via pathotyping. Genotype VII viruses have been associated with recurrent poultry outbreaks in Eastern Europe, the Middle East, and Asia and sporadic events in Africa and South America, making this large and diverse group of viruses of significant global economic importance (Miller et al., 2015). There are different numbers of genotype VII isolates recovered among locations as inferred from the GenBank public database. It is unclear if these data represent the regional prevalence or is a result of biases in sampling and reporting.

Partial fusion gene sequence data shows that sub-genotype VIIa isolates have been recovered mainly from poultry in Western Europe during the 1990s but it has been shown that there is a possibility that these viruses had Indonesian ancestors from the 1980s (Lomniczi et al., 1998). Viruses of class II genotype VII sub-genotype VIIb have been repeatedly recovered from poultry in China during 1998–2014 (Liu et al., 2002; Liu et al., 2003; Zhang et al., 2010; Zhang et al., 2014; Duan et al., 2015) with additional reports in chickens from Vietnam in 2007 and Israel in 2011–2014 (Benson et al., 2015). Many isolates were associated with outbreaks of disease in gallinaceous poultry and domestic waterfowl (Liu et al., 2003; Zhang et al., 2010; Zhang et al., 2014). Sub-genotype VIIb viruses have also been infrequently detected in peridomestic species and wild birds in China (Yuan et al., 2013; Benson et al., 2015); and these detections may be indicative of spillover from poultry into the free-ranging hosts. As evidenced from partial fusion gene sequences viruses of sub-genotype VIIb have been associated with outbreaks in poultry in Europe, Turkey, South Africa, Mozambique, Kazakhstan, the Far East, the Middle East, and India in the 1990s and in the beginning of 21st century (Herczeg et al., 1999; Abolnik et al., 2004; Bogoyavlenskiy et al., 2009; Alexander et al., 2011).

Viruses isolated from chickens and pigeons from China and Taiwan between 1996 and 2000 were placed in sub-genotypes VIIc and VIId of APMV-1 class II (Yu et al., 2001). Partial fusion gene sequence data of isolates from sub-genotype VIIc show that viruses of this sub-genotype have been also sporadically identified in poultry in Europe (Czech Republic and Switzerland) during 1996–1997 (Yu et al., 2001; Aldous et al., 2003). Sub-genotype VIId rapidly spread throughout the world and became one of the most predominant circulating genotypes since the beginning of the 21st century. Sub-genotype VIId viruses have been recovered from poultry in China (1998–2013) (Yu et al., 2001; Wan et al., 2002; Liu et al., 2003; Zhang et al., 2010; Wu et al., 2011; Zhang et al., 2014), South Korea (2000–2005) (Cho et al., 2008), and Colombia (2006–2010) (Hines et al., 2012; Benson et al., 2015). Additionally, sporadic reports

of sub-genotype VIId viruses originate from samples collected from poultry in Israel, South Africa, Ukraine, and Venezuela during 2004–2009 (Perozo et al., 2012; Dortmans et al., 2014; Benson et al., 2015). Sub-genotype VIId viruses have also been recovered from wild bird with signs of clinical disease, including the endangered crested ibis (*Nipponia nippon*), in China and various other taxa in Serbia during 2006–2007, suggesting a capacity for large mobility widespread circulation for this group of viruses and potential for spillover of viruses from poultry into wild birds (Vidanovic et al., 2011; Chen et al., 2013; Benson et al., 2015). It is unclear however, what, if any role free-ranging birds have in the maintenance and dispersal of sub-genotype VIId viruses. Apart from the geographic locations described above, partial fusion gene sequence data shows that viruses from this sub-genotype have been also isolated from poultry in Europe (Alexander, 2011), and Kazakhstan (Bogoyavlenskiy et al., 2009).

The temporal, geographic, and host distributions of sub-genotypes VIIe and VIIf viruses are similar to those of viruses in sub-genotype VIIb. Viruses of sub-genotype VIIe have been identified in chickens and domestic waterfowl in China, Japan, Taiwan, and Vietnam during 1997–2014 (Yu et al., 2001; Wan et al., 2002; Liu et al., 2003; Tang et al., 2005; Susta et al., 2011; Umali et al., 2013; Chen et al., 2015). Viruses of sub-genotype VIIf have been recovered from domestic poultry and pigeons in China during 1996–2008 (Yu et al., 2001; Liu et al., 2003; Gu et al., 2011). Viruses of sub-genotype VIIg may all represent recombinant strains (Diel et al., 2012a) and therefore are not further described in this review.

Similar to other class II genotype VII sub-genotypes, viruses of sub-genotype VIIh have also been primarily recovered from poultry. Of the relatively small number of viruses of this sub-genotype that have been recovered and genetically characterized to date, nearly all viruses have originated from chickens in Bali, Indonesia, and Malaysia during 2007–2011 (Xiao et al., 2012; Miller et al., 2015; Benson et al., 2015). The only additional virus of this subtype that has been reported and genetically characterized was recovered from a wild egret (*Ardeidae spp.*) in China (Xie et al., 2012).

The remaining sub-genotype for class II genotype VII, VIIi, may have emerged recently. Viruses of this sub-genotype have primarily been recovered from chickens in Indonesia, Israel, and Pakistan during 2010–2013, including previously vaccinated birds (Xiao et al., 2012; Rehmani et al., 2015; Benson et al., 2015). Sub-genotype VIIi viruses also caused fatal disease among koklass pheasants (*Pucrasia macrolopha*) and peafowl (*Pavo cristatus*) in Pakistan

during 2011–2012 with apparent case fatality rates of 80–100% and losses of 50–60% of susceptible birds (Munir et al., 2012b; Shabbir et al., 2012). The detection of sub-genotype VIIi viruses in previously vaccinated poultry, putative recent emergence and relatively rapid eastward spread from Indonesia to Pakistan, Israel and Eastern Europe (Fuller et al., 2015), suggest that viruses of this sub-genotype may have panzootic potential (Miller et al., 2015; Rehmani et al., 2015)

2.9. Class II genotype VIII

Few full fusion gene sequences have been reported for viruses of class II genotype VIII. Genotype VIII viruses have been recovered from chickens in Argentina, China, and Malaysia in the 1960s through 1980s (Cao et al., 2013; Murulitharan et al., 2013; Benson et al., 2015). All genotype VIII viruses are considered to be virulent. Due to lack of detection in recent decades, it is plausible that viruses of this genotype are no longer circulating among domestic birds. As inferred from the partial fusion gene sequences, class II genotype VIII viruses had also circulated in South Africa and Singapore as early as 1960s, causing outbreaks in poultry (Herczeg et al., 1999; Abolnik et al., 2004). An additional isolate of an APMV-1 viruses of this genotype was purportedly identified from turkey sampled in Italy in 1994 (Aldous et al., 2003).

2.10. Class II genotype IX

Complete fusion gene sequence information for the most ancestral virus of genotype IX originates back to an isolate recovered in China in 1940s (Liang et al., 2002; Qiu et al., 2011). Subsequent genetic information for genotype IX isolates is almost exclusively from China during 1985–2011 (Liu et al., 2003; Qiu et al., 2011; Zhang et al., 2011; Xie et al., 2013). The majority of genotype IX viruses have been detected in domestic poultry, but viruses have also been recovered from apparently healthy wild birds including whooper swan (*Cygnus cygnus*), spotted necked dove (*Streptopelia chinensis*), green peafowl (*Pavo muticus*), white-cheeked starling (*Sturnus cineraceus*), and Eurasian blackbird (*Turdus merula*) (Duan et al., 2014). Genotype IX viruses are all considered to be virulent as inferred from deduced amino acid motifs at the fusion cleavage site of respective isolates and pathotyping of representative strains (Zhang et al., 2011),

even though an ICPI value more characteristic of lentogenic strains has been obtained through pathotyping for at least one representative isolate (Duan et al., 2014).

2.11. Class II genotype X

APMV-1 isolates of class II genotype X have been recovered from wild waterfowl in the United States and Argentina during 1986–2004 (Zanetti et al., 2005; Kim et al., 2007b; Miller et al. 2009). Genotype X viruses have been inferred to be of low virulence as based upon deduced amino acid motifs at the fusion cleavage site of respective isolates (Zanetti et al., 2005; Kim et al., 2007b; Miller et al. 2009). More recently, lentogenic strains of genotype X viruses have been recovered from turkeys (*Meleagris gallopavo*) in the United States during 2008–2010 (Hines et al., 2012).

2.12. Class II genotype XI

Genotype XI viruses have been recovered from chickens in Madagascar during 2008–2011 (Maminiaina, et al., 2010; de Almeida et al., 2013). The viruses have deduced amino acid motifs suggestive of high virulence, although they have been recovered from apparently healthy, unvaccinated chickens in addition to diseased birds (Maminiaina, et al., 2010; de Almeida et al., 2013). It is possible that genotype XI viruses are transmitted across the wild bird-poultry interface in Madagascar based upon reported PCR detection of viruses from samples collected from apparently healthy wild birds (de Almeida et al., 2013), but additional information is needed to assess this possibility. Genotype XI viruses appear to have common ancestry with genotype IV viruses which may no longer be extant; however, it is unclear if this genotype has evolved in geographic isolation for decades or if these viruses are the result of relatively rapid evolution following vaccine escape (Maminiaina, et al., 2010).

2.13. Class II genotype XII

Viruses of class II genotype XII have been recovered from diseased chickens in South America in 2008–2009 (Diel et al., 2012c; Hines et al., 2012) and geese in China during 2010–2011 (Diel et al., 2012a; Sun et al., 2013). These viruses have been pathotyped as being velogenic through both the standard ICPI test and genetic characterization of isolates at the fusion cleavage site (Diel et al., 2012c; Hines et al., 2012; Sun et al., 2013). As there have not

been detections of class II genotype XII viruses in wild birds and there is a general lack of migratory connectivity between China and northern South America by free-ranging avian taxa, the epidemiologic link between outbreaks in South America and Asia remains unknown.

2.14. Class II genotype XIII

Full fusion gene sequences for class II genotype XIII viruses have been detected mainly in Eurasia and Africa and are currently divided into two sub-genotypes with the most ancestral strain being recovered from a cockatoo (family *Cacatuidae*) sampled in India in 1982 (Benson et al., 2015). Similarly to many other genotypes within class II, all viruses of genotype XIII are predicted to be virulent in chickens. Viruses of sub-genotype XIIIa have been recovered from chickens in Europe in 1997 (Linde et al., 2010), Asia during 1997–2010 (Benson et al., 2015), Africa in 1995 and 2008 (Cattoli et al., 2010), and the Middle East in 2008–2011 (Ebrahimi et al., 2012). In 2001, a sub-genotype XIIIa virus was recovered from a wild little tern (*Sterna albifrons*) in Russia suggesting potential spillover from poultry into wild birds (Usachev et al., 2006).

Sub-genotype XIIIb viruses have been recovered from India and Pakistan during 2003–2013 (Khan et al., 2010; Munir et al., 2012a; Shabbir et al., 2013; Jakhesara et al., 2014; Gogoi et al., 2015). Viruses have been isolated from chickens with the exception of a single virus strain recovered from Japanese quail (*Coturnix coturnix japonica*) in India in 2003 (Bhuvaneswari et al., 2014). The repeated recovery of sub-genotype XIIIb viruses in commercial and backyard poultry in Pakistan, including from apparently healthy birds, suggests that these viruses may be widespread in this country despite extensive vaccination efforts (Munir et al., 2012a).

2.15. Class II genotype XIV

Viruses of class II genotype XIV, which have only been recovered in West Africa, may have emerged relatively recently (de Almeida et al., 2013) and are currently divided into two sub-genotypes. All viruses from class II genotype XIV are considered to be virulent and have been isolated only from samples collected from domestic gallinaceous birds. Sub-genotype XIVa viruses have been recovered from chickens and turkeys in Niger and Nigeria during 2006–2011 (Cattoli et al., 2010; Hines et al., 2012; Van Borm et al., 2012; Snoeck et al., 2013c). Viruses of sub-genotype XIVb have been isolated from samples originating from chickens, turkeys and

guinea fowl (*Numididae spp.*) in Nigeria during 2007–2011 as well as from a single sample collected from a chicken in Benin in 2009 (Samuel et al., 2013). Given that genotype XIV viruses appear to be widespread in West Africa and that vaccination and/or prior exposure to APMV-1 strains may confer some protection against overt disease without preventing infection or viral shedding (Van Borm et al., 2012; Samuel et al., 2013; Snoeck et al., 2013c), the continued persistence and evolution of genotype XIV viruses in this region may be likely.

2.16. Class II genotype XV

The sequences of viruses of genotype XV appear to represent recombinant strains isolated from chickens and geese in China between 1997 and 2004. The existence of mixed infections of virulent viruses with vaccine viruses or wild bird viruses, and the infrequent reporting of those viruses cast doubts about their maintenance in wild or domestic birds. Therefore, the temporal, geographic, and host distribution of class II genotype XV viruses are not further described in this review.

2.17. Class II genotype XVI

APMV-1 class II genotype XVI viruses were only recently identified despite potential emergence decades prior in the northern Neotropics (Courtney et al., 2013). Genotype XVI viruses have now been identified from isolates recovered from chickens in Mexico in 1947 and the Dominican Republic during 1986–2008 (Courtney et al., 2013). All viruses have deduced amino acid motifs at the fusion cleavage site suggestive of high virulence which was confirmed for a representative strain recovered from the Dominican Republic in 2008 through *in vivo* pathotyping (Courtney et al., 2013). The large hiatus (22 years) between isolations of genotype XVI viruses suggests that viruses may have been maintained unrecognized throughout Mexico and Caribbean countries for an extended period (Courtney et al., 2013) either in vaccinated poultry or in a wild bird reservoir.

2.18. Class II genotype XVII

Similar to genotype XIV, APMV-1 viruses of class II genotype XVII have been recovered primarily from domestic poultry in West Africa during 2006–2011 (Cattoli et al., 2010; Van Borm et al., 2012; de Almeida et al., 2013; Samuel et al., 2013; Snoeck et al., 2013c).

Additionally, these viruses are also all predicted to be virulent, have been identified relatively recently, and are currently divided into two sub-genotypes. However, unlike viruses of genotype XIV, class II genotype XVII have also been recently detected in Central Africa (Cattoli et al., 2010; Snoeck et al., 2013c), which could be indicative of viral spread across the continent.

APMV-1 viruses of class II genotype XVII sub-genotype XVIIa have been recovered and genetically characterized from chickens in Benin, Burkina Faso, Cameroon, Ivory Coast, Mali, Niger, and Nigeria during 2006–2011 (Cattoli et al., 2010; Van Borm et al., 2012; de Almeida et al., 2013; Samuel et al., 2013; Snoeck et al., 2013c). In comparison to sub-genotype XVIIa, fewer sub-genotype XVIIb viruses have been recovered and genetically characterized, all of which originated from chickens in Nigeria during 2006–2011 (Cattoli et al., 2010; Snoeck et al., 2013c; Susta et al., 2014b).

2.19. Class II genotype XVIII

Viruses of class II genotype XVIII share similarities with those of genotypes XIV and XVII. Specifically, genotype XVIII viruses are considered to be virulent, may have recently emerged, have been recovered primarily in domestic birds in West Africa, and are currently divided into two sub-genotypes. Viruses of sub-genotype XVIIIa have been recovered and genetically characterized from chickens and guinea fowl sampled in the Ivory Coast, Mali, and Mauritania during 2006–2010 (Cattoli et al., 2010; de Almeida et al., 2013; Snoeck et al., 2013c). Similarly, sub-genotype XVIIIb strains have been isolated from poultry in the Ivory Coast, Mali, Nigeria, and Togo (Cattoli et al., 2010; de Almeida et al., 2013; Samuel et al., 2013; Snoeck et al., 2013c) as well as a wild village weaver (*Ploceus cucullatus*) in the Ivory Coast (Snoeck et al., 2013a). Collectively, this information suggests that genotype XVIII viruses may be widespread in poultry in the region that spillover events into wild birds may occur.

3. Conclusions

The large diversity of temporal, geographic, and host distribution of genotypes containing virulent and non-virulent strains of APMV-1 suggests that many factors may contribute to the maintenance, evolution, and dispersal of this viral agent. It is possible that a complex combination of selection pressures may promote the development of genetic variants able to exploit both wild and domestic hosts. For instance, despite presumed disproportional sampling of

diseased poultry, numerous genotypes and sub-genotypes of APMV-1 have been detected in both wild and domestic birds. The presence of identical genotypes/sub-genotypes in wild birds and poultry supports transmission across the wild bird-poultry interface (e.g., class I; class II genotypes I, II, VII and IX). APMV-1 may, therefore, be subject to selection pressures in free-ranging hosts and modern food production systems.

With a few exceptions (e.g., genotypes I, II, X), APMV-1 isolates do not display evidence of change in virulence within a genotype. Since the identification of APMV-1 in 1926, few changes in virulence have been reported for viruses within a given genotype with most reports of new viruses displaying similar virulence as progenitors. For two genotypes of virulent viruses, a potential free-ranging avian reservoir has been suggested (i.e. double-crested cormorants [sub-genotype Va] and Columbids [genotype VI]). It is unclear if similar free-ranging reservoirs exist for other virulent genotypes or if these viruses are maintained in poultry. Although lentogenic viruses of class I and class II genotypes I and II have also been associated with specific taxonomic groups of birds (i.e. waterfowl) these viruses have also been isolated from a wide range of hosts. It is therefore possible that the virulence of the APMV-1 may be associated with the ability of viruses to be maintained in a specific host population. Thus, low virulence viruses, which generally do not cause disease, may be maintained in a broad diversity of species whereas virulent viruses may only be maintained in host populations in which clinical disease is minimal (e.g., asymptomatic wild birds or vaccinated poultry). However, since many APMV-1 isolates from wild birds have resulted from sampling efforts for influenza A viruses, sampling biases may still be a factor that limits inference on the host distribution of APMV-1 genotypes in wild birds.

Recent phylogenetic analyses of APMV-1 isolates report larger genetic diversity than previously recognized. Therefore, it appears that vaccination and biosecurity practices to control APMV-1 may have a limited impact towards viral eradication, particularly in some endemic countries, despite widespread application of measures to control outbreaks and minimize disease. It is unclear if these findings are likely a function of increased sampling effort in certain regions of the world, changing selective pressures for viruses, or a combination of both. The recent identification of new viral genotypes (e.g., class II genotypes XIII, XIV, XVI, XVII, and XVIII) as well as the apparent continued circulation of viruses identified decades ago (e.g., class II

genotypes I, II, V, IX, and X) suggests that the increasing global population of domestic poultry may provide ample opportunities for continued viral maintenance and evolution.

Finally, while some APMV-1 genotypes appear to be globally widespread (e.g., class I; class II genotypes I, II, VI and VII), others have more regional geographic ranges within continents (e.g., class II genotypes XI, XIII, XIV, XVI, XVII, and XVIII). Although viral dispersal is likely a complex function of numerous factors including time since emergence, host adaptation, and infectivity, evidence suggests that human activities and bird migration both have the potential to promote the intercontinental spread of some APMV-1 genotypes (e.g., class I; class II genotype VI). Furthermore, the large genetic distances of some more recently identified genotypes suggests that they might have evolved undetected for many years despite contemporary sampling efforts. There is a need to increase the collection of field isolates combined with data on host distribution. This information and the relative rate of regional/continental dispersal, may help to better understand the panzootic potential of APMV-1 of different genotypes.

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Appendix A. Supplementary data

Figures Legend:

Fig. 1. Phylogenetic tree constructed using the complete nucleotide sequences of the fusion gene of representative isolates of *Avian paramyxovirus 1* class I and class II.

The evolutionary history was inferred by using the Maximum Likelihood method based on the General Time Reversible model as implemented in MEGA6 (Nei and Kumar, 2000). The tree with the highest log likelihood (-25365.2332) is shown. Initial trees for the heuristic search were obtained by applying the Neighbor-Joining method to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach. A discrete Gamma distribution was used to model evolutionary rate differences among sites (4 categories (+G, parameter = 0.7327). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 87 nucleotide sequences. Codon positions included were 1st, 2nd, 3rd, and non-coding. All positions containing gaps and missing data were eliminated. There were a total of 1651 positions in the final dataset. Evolutionary analyses were conducted in MEGA6 (Tamura et al., 2013).

Table 1. Estimates of genetic distances between class I and class II genotypes

Figure S1. Phylogenetic analysis based on the complete nucleotide sequence of the fusion gene of isolates representing *Avian paramyxovirus 1* class I and class II.

The evolutionary history was inferred by using the Maximum Likelihood method based on the General Time Reversible model as implemented in MEGA6 (Nei and Kumar, 2000). The tree with the highest log likelihood (-97131.4001) is shown. Initial trees for the heuristic search were obtained by applying the Neighbor-Joining method to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach. A discrete Gamma distribution was used to model evolutionary rate differences among sites (4 categories (+G, parameter = 0. 9238). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 1491 nucleotide sequences (Supplementary Table 1). Codon positions included were 1st, 2nd, 3rd, and non-coding. All positions containing gaps and missing data were eliminated. There were a total of 1646 positions in the final dataset. Evolutionary analyses were

conducted in MEGA6 (Tamura et al., 2013). Roman and Arabic numerals and lowercase letters in front of taxa names represent genotype designation.

Table S1. Class I and class II complete fusion gene sequences used for constructing ML phylogenetic tree presented in Figure S1.

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Table(s)

Table 1. Estimates of evolutionary distances between class I and class II genotypes[1,2]

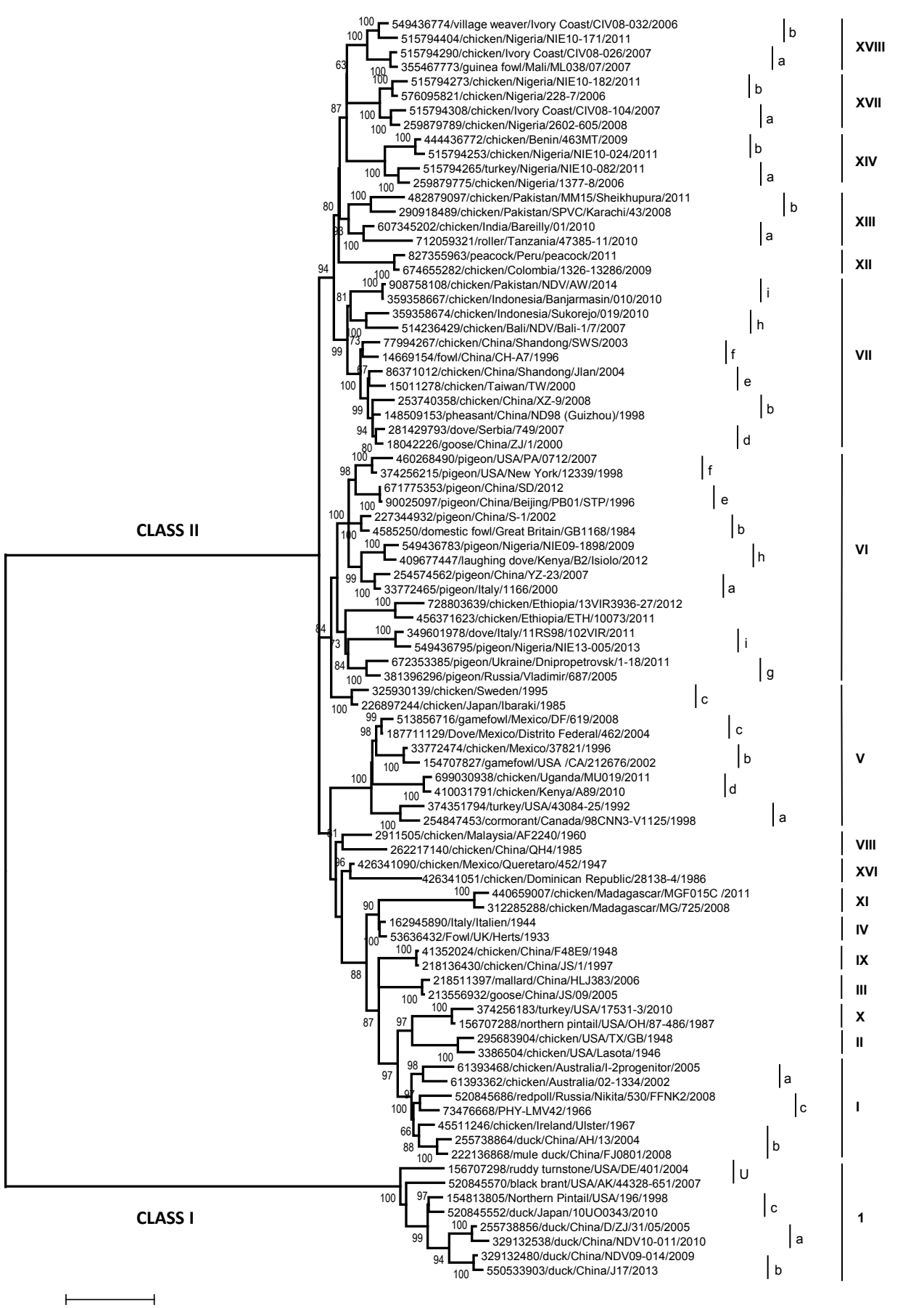
	Genotype (number of analyzed sequences)	No. of base substitutions per site (SE)[3]															
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XVI	XVII	XVIII
CLASS II	I (n=136)																	
	II (n=154)	0.129																
	III (n=8)	0.115	0.144															
	IV (n=4)	0.102	0.131	0.082														
	V (n=87)	0.192	0.211	0.181	0.147													
	VI (n=222)	0.189	0.210	0.184	0.140	0.165												
	VII (n=460)	0.187	0.218	0.179	0.143	0.164	0.139											
	VIII (n=5)	0.145	0.169	0.136	0.097	0.131	0.124	0.129										
	IX (n=25)	0.107	0.132	0.094	0.078	0.173	0.177	0.173	0.127									
	X (n=11)	0.119	0.122	0.143	0.129	0.212	0.207	0.209	0.167	0.129								
	XI (n=14)	0.202	0.231	0.192	0.128	0.232	0.240	0.248	0.200	0.173	0.227							
	XII (n=8)	0.197	0.234	0.189	0.155	0.171	0.136	0.125	0.132	0.187	0.216	0.254						
	XIII (n=40)	0.186	0.218	0.184	0.144	0.166	0.144	0.122	0.129	0.171	0.208	0.237	0.116					
	XIV (n=50)	0.226	0.266	0.229	0.185	0.195	0.177	0.153	0.161	0.224	0.240	0.289	0.143	0.142				
	XVI (n=4)	0.164	0.194	0.159	0.117	0.161	0.158	0.166	0.117	0.152	0.184	0.224	0.168	0.159	0.195			
	XVII (n=48)	0.183	0.225	0.190	0.153	0.171	0.156	0.137	0.143	0.177	0.216	0.235	0.127	0.120	0.135	0.176		
	XVIII (n=16)	0.191	0.220	0.186	0.149	0.170	0.142	0.129	0.137	0.176	0.211	0.238	0.123	0.116	0.137	0.168	0.108	
CLASS I genotype 1 (n=199)		0.412	0.441	0.423	0.429	0.448	0.444	0.451	0.431	0.439	0.410	0.463	0.440	0.436	0.450	0.432	0.437	0.412

[1]Inferred from the complete nucleotide F gene sequence

[2]The isolates from genotype XV appear to represent recombinant strains and are not included in this analysis.

[3]The number of base substitution per site from averaging all sequence pairs between class II genotypes is shown. Values in parentheses above the diagonal are standard error estimates, obtained by a bootstrap procedure (500 replicates). Analyses were conducted using the Maximum Composite Likelihood model [Tamura et al., 2004]. The rate variation among sites was modeled with a gamma distribution (shape parameter = 1). The analysis involved 1491 nucleotide sequences. Codon positions included were 1st, 2^{nd,} 3rd and noncoding. All positions containing gaps and missing data were eliminated. Evolutionary analyses were conducted in MEGA6 (Tamura et al., 2013). Shaded cells represent inter-genotype nucleotide distances that are lower than 10%.

Figure(s)


sub-genotype
GENOTYPE
549436774/village weaver/Ivory Coast/CIV08-032/2006
515794404/chicken/Nigeria/NIE10-171/2011
515794290/chicken/Ivory Coast/CIV08-026/2007
355467773/guinea fowl/Mali/ML038/07/2007
515794273/chicken/Nigeria/NIE10-182/2011
576095821/chicken/Nigeria/228-7/2006
515794308/chicken/Ivory Coast/CIV08-104/2007
259879789/chicken/Nigeria/2602-605/2008
444436772/chicken/Benin/463MT/2009
515794253/chicken/Nigeria/NIE10-024/2011
515794265/turkey/Nigeria/NIE10-082/2011
259879775/chicken/Nigeria/1377-8/2006
482879097/chicken/Pakistan/MM15/Sheikhupura/2011
290918489/chicken/Pakistan/SPVC/Karachi/43/2008
607345202/chicken/India/Bareilly/01/2010
712059321/roller/Tanzania/47385-11/2010
827355963/peacock/Peru/peacock/2011
674655282/chicken/Colombia/1326-13286/2009
908758108/chicken/Pakistan/NDV/AW/2014
359358667/chicken/Indonesia/Banjarmasin/010/2010
359358674/chicken/Indonesia/Sukorejo/019/2010
514236429/chicken/Bali/NDV/Bali-1/7/2007
77994267/chicken/China/Shandong/SWS/2003
14669154/fowl/China/CH-A7/1996
86371012/chicken/China/Shandong/Jlan/2004
15011278/chicken/Taiwan/TW/2000
253740358/chicken/China/XZ-9/2008
148509153/pheasant/China/ND98 (Guizhou)/1998
281429793/dove/Serbia/749/2007
18042226/goose/China/ZJ/1/2000
460268490/pigeon/USA/PA/0712/2007
374256215/pigeon/USA/New York/12339/1998
671775353/pigeon/China/SD/2012
90025097/pigeon/China/Beijing/PB01/STP/1996
227344932/pigeon/China/S-1/2002
4585250/domestic fowl/Great Britain/GB1168/1984
549436783/pigeon/Nigeria/NIE09-1898/2009
409677447/laughing dove/Kenya/B2/Isiolo/2012
254574562/pigeon/China/YZ-23/2007
33772465/pigeon/Italy/1166/2000
728803639/chicken/Ethiopia/13VIR3936-27/2012
456371623/chicken/Ethiopia/ETH/10073/2011
349601978/dove/Italy/11RS98/102VIR/2011
549436795/pigeon/Nigeria/NIE13-005/2013
672353385/pigeon/Ukraine/Dnipropetrovsk/1-18/2011
381396296/pigeon/Russia/Vladimir/687/2005
325930139/chicken/Sweden/1995
226897244/chicken/Japan/Ibaraki/1985
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33772474/chicken/Mexico/37821/1996
154707827/gamefowl/USA /CA/212676/2002
699030938/chicken/Uganda/MU019/2011
410031791/chicken/Kenya/A89/2010
374351794/turkey/USA/43084-25/1992
254847453/cormorant/Canada/98CNN3-V1125/1998
2911505/chicken/Malaysia/AF2240/1960
262217140/chicken/China/QH4/1985
426341090/chicken/Mexico/Queretaro/452/1947
426341051/chicken/Dominican Republic/28138-4/1986
440659007/chicken/Madagascar/MGF015C /2011
312285288/chicken/Madagascar/MG/725/2008
162945890/Italy/Italien/1944
53636432/Fowl/UK/Herts/1933
41352024/chicken/China/F48E9/1948
218136430/chicken/China/JS/1/1997
218511397/mallard/China/HLJ383/2006
213556932/goose/China/JS/09/2005
374256183/turkey/USA/17531-3/2010
156707288/northern pintail/USA/OH/87-486/1987
295683904/chicken/USA/TX/GB/1948
3386504/chicken/USA/Lasota/1946
61393468/chicken/Australia/I-2progenitor/2005
61393362/chicken/Australia/02-1334/2002
520845686/redpoll/Russia/Nikita/530/FFNK2/2008
73476668/PHY-LMV42/1966
45511246/chicken/Ireland/Ulster/1967
255738864/duck/China/AH/13/2004
222136868/mule duck/China/FJ0801/2008
156707298/ruddy turnstone/USA/DE/401/2004
520845570/black brant/USA/AK/44328-651/2007
154813805/Northern Pintail/USA/196/1998
520845552/duck/Japan/10UO0343/2010
255738856/duck/China/D/ZJ/31/05/2005
329132538/duck/China/NDV10-011/2010
329132480/duck/China/NDV09-014/2009
550533903/duck/China/J17/2013
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