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Review

Review of companion animal viral diseases and immunoprophylaxis

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ABSTRACT

In this article we review important established, newly emergent and potential viral diseases of cats, dogs and rabbits. Topics covered include virus epidemiology, disease pathogenesis, existing and prospective immunoprophylaxis against the viruses. For some feline viruses, notably the immunodeficiency virus, leukaemia virus and peritonitis virus, available vaccines are poorly efficacious but there are good prospects for this. A further challenge for the industry is likely to be due to viruses jumping species and the emergence of more virulent variants of established viruses resulting from mutations as has been the case for the canine parvovirus, coronaviruses and feline calicivirus.

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Contents

1. Introduction

Viruses of many families cause disease in small companion animals and there is much academic and industrial interest in understanding disease pathogenesis, virus transmission in the field and prophylactic control of diseases. Companion animal viral vaccines represent a significant share of the global veterinary vaccines market to which several manufacturers offer products. Most products, however, are formulated using old vaccine viral strains which in some instances, are in need of updating in view of emergence of more virulent strains in the field. Pathogenic mutants with altered organ tropism have for instance emerged in case of carnivore par-

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vovirus, calicivirus and coronavirus. Hence there is, in our view, the need for an appraisal of the current status of the new viral mutants and associated diseases and current and prospective vaccines. Important areas considered in viral family are epidemiology of infections particularly mode of virus transmission, associated diseases and key determinants in disease pathogenesis. Current immunoprophylaxis in relation to prospects of improved and safer vaccines and some difficulties in achieving these objectives for particular viral diseases are reviewed as well. Newly emerging and potential diseases are discussed in the last section. The companion animals presently considered are cats, dogs and rabbits. Unusual pets such as ferrets, mice, hamsters and snakes in view of the enormity of the task were considered out of scope. Horses [1–3] and pigeons [4] have already been covered recently.

2. DNA viruses

2.1. Herpesviridae

Herpesviruses are enveloped, icosahedral viruses with a linear double stranded DNA. Taxonomically, members have been placed in three subfamilies, alpha, beta and gammaherpesvirinae based on their biology [5]. An important characteristic of investigated mammalian and avian herpesviruses is their ability to establish latency and remain latent in their primary host for life and recrudesce from latency in response to certain stimuli and be shed. In latent state, multiple copies of viral DNA are demonstrateable as episomes without active synthesis of viral proteins and precursors. Alphaherpesviruses tend to frequently but not exclusively, become latent in neural cells of cranial or sacral ganglia, the beta and the gammaviruses in lymphoid cells. Distinct herpesviruses cause disease in cats and dogs while rabbits may not be the natural host to significant herpesvirus disease. However, rabbits have been used as models to study disease pathogenesis of some alphaherpesviruses [6] and also gammaherpesvirus [7,8].

Canine alphaherpesvirus-1 (CHV-1) was first identified in USA in 1965 as the cause of a highly fatal, generalised hemorrhagic disease in pups less than 4 weeks of age (fading puppy disease) and has subsequently been detected in most countries where diagnosis was undertaken. However, CHV-1 prevalence in the dog population as a whole is low [9], although it may be highly prevalent in kennels. CHV-1 spreads by aerosol and initiates infection in the oropharyngeal mucosa and the local lymph nodes and results in reticuloendothelial cell viraemia. In puppies less than 3 weeks of age, viraemia disseminates the virus systemically and after replication in organs, causes widespread petechiation in the liver, kidneys, lungs and lymph nodes. Severely affected puppies may die. In adult dogs, CHV-1 infection is less severe and may cause cough and dyspnoea in individuals with generalised infection of the bronchial tree and may be part of the kennel cough syndrome and/or reproductive failure.

The cat alphaherpesvirus-1 (FHV-1) is also transmitted by aerosol followed by viral replication in nasal and conjunctival epithelium and subsequent dissemination of progeny virus throughout the bronchial tree. Typical clinical signs of FHV-1 infection are rhinitis, bronchitis, conjunctivitis, nasal discharge, dyspnoea, fever, coughing and inappetence. The FHV-1 disease has some clinical similarities to FCV respiratory disease and is commonly referred to as feline viral rhinotracheitis (FVR). Secondary bacterial bronchopneumonia, commonly in kittens but rarely in older cats, may result in death. Experimentally, both FHV-1 and CHV-1 were found to cause vaginitis. The incubation period for the common disease signs for both viruses is 1–2 days.

2.2. Adenoviridae

Adenoviruses were first named in 1956 to cluster a new group of cytopathic viruses recovered from explanted human adenoid and tonsillar tissue. The family has two genera, the mastaadenoviruses from mammals and aviadenoviruses from birds. Genera are further classified into subgenus, species and strains. Adenoviruses cause disease in dogs and pigeons. Two antigenically related adenoviruses species can cause significant disease in domestic dogs and other canids. The two viruses involved are commonly known as canine adenovirus-1 (CAV-1) and 2 (CAV-2) and also as infectious canine hepatitis virus and infectious canine laryngotracheitis virus respectively. The close antigenic cross-reactivity is seen at the level of significant reciprocal but unequal cross-neutralisation. The viruses are however unequivocally distinguished by DNA fingerprinting of endonuclease digests of viral DNA. CAV-1 occurs worldwide and infects and replicates in oropharynx after the ingestion of infectious material from respiratory secretions, urine or faeces. The primary replication in tonsils, Peyers patches and epithelia of oropharynx and bowel results in lymphoid cell viraemia which initiates secondary infection of parenchyma of liver, kidney and lining of blood vessel and sinusoids in these organs and other sites. Infected cells die and lyse leading to mainly pinpoint bleeds and haemorrhages and some times a large bleed if a major vessel is involved. CAV-1 causes fatal hepatitis in newly weaned puppies and susceptible young dogs. Other lesions due to CAV-1 infection comprise subcutaneous oedema, ascites and oedema of the gall bladder wall, immune complex keratitis and nephritis. Older dogs may be susceptible but signs are milder with enlargement of tonsils, sub-maxillary lymph nodes and sometimes immune complex keratitis. Isolates of CAV-1 vary in virulence for the domestic dog, some cause sub-clinical diseases while others acute disease with severe abdominal pain followed by death. Wild and farmed dogs are highly susceptible to some strains of CAV-1 encephalitis. CAV-1 can often cause immune complex vasculitis, commonly known as blue eye.

CAV-2 transmission among dogs is mainly by inhalation and virus is widely prevalent. CAV-2 is a major cause of kennel cough syndrome. CAV-2 causes extensive lesions in the upper and the lower respiratory tract resulting in interstitial pneumonia often with necrotising bronchitis and bronchiolitis, focal necrosis of the turbinate and tonsillar epithelium. The disease is more severe when associated with concurrent bacterial infection. Often the bronchial nodes are congested and haemorrhagic but gross liver and gall bladder lesions are usually absent. CAV-2 infection in dogs has not been associated with hepatitis. Other signs of CAV-2 infection may be fever, mild depression and nasal and/or ocular discharge; corneal opacity is sometimes seen.

2.3. Poxviridae

Members are large, enveloped, highly resistant viruses with a double-stranded linear DNA genome which replicates in cytoplasm of infected cells. The subfamily *Chordopoxvirinae* has members affecting vertebrates classified into six genera [10]. The vertebrate poxviruses usually produce proliferative focal lesions and are occasionally fatal when they generalise. Members are very stable and virus shed in scabs survives for months or years in dust particularly in dry conditions. Companion animal species affected by poxviruses are rabbits, pigeons and mild disease due to cowpoxvirus has been reported in cats. Myxomavirus (MV) in genus leporipoxvirus causes myxomatosis, a systemic and usually a fatal disease in European rabbits (*Oryctolagus cuniculus*) but a benign disease in its natural host, Sylvilagus rabbits in the Americas [11,12]. MV spreads mechanically by blood-feeding arthropod vectors such as mosquitoes and fleas and to a lesser degree by direct contact

or aerosol [9]. Virus remains infectious for several months in vectors. In rabbit MV replicates subcutaneously locally followed by viraemia and generalised dissemination to connective tissue cells initiating a proliferative response and exudative erythematous dermatitis around the face, eyes and skin surfaces generally. The lesions become ulcerated and covered with weeping crusts [11,12]. Field epizootics have resulted in mortality rates approaching 100%.

Cats occasionally become infected with a poxvirus which is indistinguishable from cow poxvirus in genus orthopoxvirus. Infection in cats is acquired from rodent bites and develops as small red macular eruptions which develop into papules or ulcers which scab over several days on the legs and/or head which in some infected cats become more widespread and may spread to lungs.

2.4. Parvoviridae

Members are the smallest, along with circoviruses, of DNA viruses and include important pathogens of cats and dogs. Parvoviruses and circoviruses have a predilection for replication in rapidly dividing cells of bone marrow, enteric epithelium and the foetus. A parvovirus with predilection for rabbit small intestine and lymphoid tissues and liver has been known for sometime but the virus does not appear to be a significant rabbit pathogen and only causes mild catarrhal enteritis [13]. Members have an icosahedral capsid with an over all diameter of 18–25 nm and contain linear, single-stranded DNA.

The known carnivore parvoviruses named feline panleukopenia virus (FPLV), canine parvovirus (CPV-types 1, 2, 2a, 2b and 2c), mink enteritis virus (MEV-types 1, 2 and 3) and those isolated from wild felids and canids such as raccoons, foxes (red and blue species), leopards and cheetahs are genetically related and interspecies transmissions among carnivores occur readily [14,15]. CPV-2 was first recognised in 1978 as the cause of new disease in dogs which rapidly spread worldwide [16–19]. Evidence suggests that the CPV arose from the long recognised FPLV or related virus infecting another carnivore such as mink, raccoon, artic fox or other. The new virus differed from FPLV like viruses in less than 1% in genomic sequence [20–23]. However, the life of firstly identified CPV variant in nature was brief [24]. By 1981 CPV-2 was replaced by CPV-2a which in turn was replaced between 1984 and 1990 by CPV-2b. In each case the replacement was global. Interestingly, CPV-2 and its 2a and 2b variants differed by less than 0.2% in their genome sequence and involved substitution of 3–4 amino acids in virus capsid protein VP2 [20–23,25]. This change was ongoing with the identification of CPV-2c in late 1990s [26]. The latter variant has also spread widely [27]. CPV-2c has one amino acid substitution in VP2 [26]. Whilst this change in VP2 is minor it was nonetheless significant in conferring a broader host range phenotype to the variants. Thus experimentally cats were refractory to infection by CPV-2 but readily susceptible to infection by CPV-2a and 2b viruses [23]. These viruses occur worldwide and are evolving rapidly [28,15,29]. However, their evolutionary history is complex and possibly not fully unravelled and it has been suggested that their current classification and naming of new isolates needs revision [15].

A key factor in the epidemiology and evolution of carnivore parvoviruses has been the virus tropism for the gut and the survival of virus shed in faeces for long periods (several months to 2 years). Faecal-oral route is the main mode of virus transmission of these important carnivore viruses. However, in vivo tissue tropism of FPLV and CPV vary with respect to ability to replicate in enteric epithelium and produce faecal virus in quantity. In cats FPLV replicates in lymph nodes, thymus, spleen and intestine and large quantities are shed in faeces while in dogs FPLV replication occurs in the thymus and bone marrow but not in the gut and mesenteric lymph node [30]. CPV and FPLV also initiate infection in the mucosa and lymphoid tissue of the buccal cavity and result in leukocyte-associated viraemia followed by progeny virus spread to internal organs. In puppies ingested virus replicates in crypts of small intestine resulting in leukocyte viraemia, viral dissemination and secondary infection of the liver and of cardiac myocytes although the latter is rarely seen today due to effective vaccination. Infection of these vital organs may cause eventual heart failure associated with pulmonary oedema, hepatomegaly and ascites. Mortality is high. In older dogs ingested virus replicates in intestinal crypts which more commonly results in vomiting, diarrhoea and leucopoenia with high morbidity but low mortality.

Pathogenesis of FPLV infection in cats is similar to CPV disease in dogs. Viraemia following the respiratory and the enteric phases of viral replication leads to secondary infection of bone marrow, spleen and lymph nodes. This results in transient leukocytosis followed by a marked leucopoenia and anaemia. Virus is shed by most routes 2–6 days after infection.

3. RNA viruses

3.1. Caliciviridae

Members are non-enveloped icosahedral very small (27–40 nm) viruses with a linear, positive sense single stranded RNA genome and replicate in cell cytoplasm. Three viral species in family Caliciviridae cause significant diseases in cats, rabbits and brown hares. Feline calicivirus (FCV) belongs to the distinct phylogenetic clade in genus vesivirus. Rabbit haemorrhagic disease virus (RHDV) and European brown hare syndrome virus (EBHSV) belong to the distinct phylogenetic clade in genus lagovirus. RHDV and EBHSV share antigenic epitopes which elicit cross-protective antibodies. Caliciviruses are not considered significant pathogens of domestic dogs nor are they isolated frequently. However both FCV related and unrelated caliciviruses have been isolated from faeces of puppies and dogs with diarrhoea [31–33]. Canine caliciviruses (CCoV) at present remain unclassified [34]. However, it is possible that one or more of these dog isolates of caliciviruses have the potential to adapt, spread and establish in dog populations to cause clinically important disease. Caliciviruses do mutate readily in nature as is indicated by the emergence of a highly virulent haemorrhagic variant of FCV [35–37] which has spread rapidly [38,39]. The newly emergent FCV variants have been named virulent systemic FCV (VS-FCV) to distinguish them from the common FCV strains. FCV has a worldwide distribution while VS-FCV is, at present, limited to USA and the UK [36] but very likely to become more prevalent. VS-FCV strains appear to have arisen independently of one another and have not spread from a single case [37]. Both virus types are excreted in urine, saliva, ocular and respiratory secretions and are transmitted via aerosol, orally and on fomites. Usually, virus shedding is for up to 2 weeks but some recovered cats shed the virus intermittently [40]. Primary infection by both virus types is often in the upper respiratory tract and/or oral mucosa with an incubation period of 2–3 days resulting in epithelial cell necrosis with vesicle or ulceration of the external nares and oral mucosa. Virulent FCV strains may also cause interstitial pneumonia. Infected cats may also manifest fever, anorexia, conjunctivitis, lethargy and stiffness, nasal and ocular discharge, sneezing and rales. Some FCV but most VS-FCV strains are fatal [35,36].

RHDV and EBHSV infections are highly contagious and acute fatal diseases caused by distinct but antigenically related caliciviruses. RHD was first reported in the People's Republic of China in imported Angora rabbits imported from German Democratic Republic [41] while EBHS was described in brown hares (*Lepus europeus*) and mountain hares (*Lepus timidus*) in 1981 in Sweden [42]. However, epidemiological investigations indicated presence

of these viruses in Europe much before the above published reports. One line of data supporting this conclusion was the detection of RHDV antibodies in rabbit sera collected in early 1970s [43]. RHDV is endemic in most parts of Europe, Asia and parts of Africa, Australia and New Zealand. RHDV was imported into Australia in 1991 for biological control of wild rabbits but the virus escaped from Wardang island quarantine facility in 1995 and became established across Southern Australia [44]. Insect vectors were suspected as to have spread the virus from Wardang Island [45]. EBHSV is widespread wherever hares (*L. europeus* and sub species) are endemic as is the case in Europe [46]. Rabbit species vary in their susceptibility to RHDV infection. American cottontail rabbits (*Sylvilagus floridanus*) appear to be refractory to infection by RHDV [47,48]. RHDV transmission is by direct contact and via fomites [45]. Thus primary infection is at an oral and/or conjunctival mucosa. EBHSV is likely to be similarly transmitted among hares. Flies of the genus Phormia in Europe transmit RHDV via the conjunctiva while in Australia bush flies (*Musa vestustissima*) and blow flies (*Caliphora dubia*) were identified as potential vectors [49,50,45]. Rabbit fleas (*Siplopsyllus cuniculi* and *Xenopsylla cunicularis*) and mosquitoes (*Culex annulirostris*) were shown to transmit RHDV to rabbits under laboratory conditions [51,45]. Molecular epidemiological studies, thus far, have shown a low (less than 10% nucleotide) genomic variation among RHDV isolates collected over a period of several years from different geographical areas [52,53]. However, natural mutational changes in the field have been recorded [54]. A question that remains unresolved is that of how virus persists in nature from year to year. Typically in the field RHDV infected rabbits die within 24–48 h with few outward signs excepting bloody mucous discharge from the nose.

Following the primary replication in oronasal and/or ocular mucosa RHDV infects macrophages and other mononuclear cells (circulatory and alveolar macrophages) and these infected cells disseminate the virus to the internal organs particularly the liver and kidneys where virus undergoes secondary replication [55]. Cells of the mononuclear phagocyte lineage are also likely to be involved in transmission of EBHSV to the internal organs of infected hares. In both RHD and EBHS, a consistent finding is severe necrotising hepatitis, characteristic lesion being coagulation liver necrosis in RHD and lytic necrosis in EBHS [56]. However, the two diseases also have characteristic pathological differences. In RHD, disseminated intravascular coagulation (DIC) and thrombi in kidneys and lungs are common lesions while DIC has not been observed in hares with EBHS and haemorrhages are also infrequent [56]. Depletion of splenic lymphocytes is observed in both diseases. Apoptosis of hepatocytes, macrophages and endothelial cells along with DIC and progressive jaundice are common features in RHD of rabbits [57]. An interesting hypothesis put forward to explain the differences in types of lesions between RHD and EBHS was suggested as due to the genetic difference between the two affected lagomorphs species. Evidence supporting this hypothesis has been the observation of liver lesions in RHDV infected hares that were indistinguishable from those seen following EBHSV disease of hares [56]. Thus the type of lesions is apparently not determined by the virus species. As in FCV infection of cats, protection against RHDV disease is conferred by virus neutralising antibody to the major viral capsid protein namely VP60 in RHDV.

3.2. Coronaviridae

Coronaviruses (CoVs) (family Coronaviridae, order Nidovirales) are a group of enveloped positive-strand large RNA viruses of mammals and birds and are found worldwide. The coronavirus genus has been classified into three clusters or groups based on antigenic cross reactivity and other criteria. Group 1 has dog (CCoV), cat (FCoV), human (HCoV-229E), pig epidemic diarrhoea (PEDV), pig respiratory (PRCoV), pig transmissible gastroenteritis (TGEV) CoVs. Group 2 species are bovine (BCoV), human (HCoV-OC43), mouse (MHV), pig haemagglutinating encephalomyelitis (HEV), SARS (SARS-CoV), canine respiratory coronavirus (CRCoV) and other CoVs. Group 3 consists exclusively of avian CoVs. Most members usually cause mild enteric and/or respiratory disease and hence are generally considered of minor clinical importance. There are however exceptions (see below). The large genome is prone to high frequency mutations [58–60]. CoVs have the potential to jump the species barrier and cause severe disease as was the case for severe acute respiratory syndrome (SARS) in Southern China [61]. Studies by different groups demonstrated that SARS-CoV succeeded in spillover from a wildlife reservoir (probably bats) to human population via an intermediate host(s) and that rapid viral evolution played a key role in the adaptation of SARS-CoVs in at least two non-reservoir species within a short period [62]. It has been shown that cats and ferrets can be infected with this virus as well [63]. Virus transmission is by inhalation and/or ingestion of virus in faeces, saliva and aerosol. This results in limited virus replication in upper respiratory tract (URT) and/or intestinal mucosa and associated lymphoid tissues and progeny virus does not normally or only limitedly generalises to internal organs with some exceptions. However combined secondary bacterial infection often exacerbates the clinical disease. Dogs are susceptible to two CoVs, the enteric (CCoV) [64] and the newly recognised respiratory CoV (CRCoV) [65,66]; the latter virus has been placed in antigenic group 2 along with BCoV and others. The group 1 CCoVs have been placed into two serotypes (I and II). CCoVs primarily cause mild enteric disease in puppies manifest as fever, depression, anorexia and diarrhoea. Severe disease due to CCoV is infrequent [60]. However, a pantropic virulent variant of serotype II CCoV with much broader viscerotropic phenotype was recognised recently [67]. This variant (designated CB/05), in addition to the usual enteric replication, also spreads to and replicates in internal organs (lungs, spleen, liver, kidney and brain) and was the cause of deaths of some dogs [67–69].

FCoVs occur as two serotypes with different serological and biological characteristics, particularly in sequence homology of the viral surface S glycoprotein [59]. Like CCoVs, most FCoVs cause mild enteric disease but could give rise to highly pathogenic variants in individual infections causing peritonitis (FIP). Both serotypes of FCoV mutate to virulent FIPV variants. Their relative prevalence in nature varies but type I FIPV/FCoV strains are generally dominant in the field [70]. FIPV variants of FCoV have been the cause of fatal peritonitis in some cases [71,72]. FCoVs are transmitted via the faecal-oral route and primarily replicate in enterocytes [73] from where the progeny virus disseminates to internal organs via monocyte-associated viraemia. Although FCoV is highly prevalent, FIP morbidity is relatively low, rarely exceeding 5% [73]. Feline infectious peritonitis (FIP) is a progressive debilitating disease. A pathognomic feature of FIP is widespread occurrence of pyogranulomatous lesions in majority of organs (lungs, liver, spleen, omentum and brain) and other tissues [74,75]. Other features of FIP involve a marked T-cell depletion, particularly in end-stage FIP [76] and hypergammaglobulinemia [77]; B-cell leucopoenia is also a feature in FIP disease [78]. The T-cell depletion is apparently not the result of virus infection since T-cells appear not to support virus replication [76]. Other important determinants in FIP pathogenesis appear to be (i) dissemination of mutant progeny FIPV by activated macrophages and monocytes and their availability [79] and (ii) types of viral S protein neutralising antibodies at suboptimal concentration which opsonise the virus and enhance its infectivity for target cells via Fc receptor mediated attachment [80–82]. There is also complement activation with resultant platelet aggregation, intravascular coagulation necrotising lesions and exudation of fluid

into the abdomen and thoracic cavity in the so-called wet form of FIP. Wet FIP is most common in kittens under one year of age and the incidence declines by 5 years of age when the dry form of FIP is more common [82]. Whilst there is no protective immunity in wet FIP, the dry form is a result of partial immunological protection [82–83]. Some of these pathogenetic features of FIP notably the T-cell lymphopenia, multiphasic disease course and viral persistence have been seen in SARS. Both these diseases are an enigma possibly stemming from virus-induced immune dysregulation.

3.3. Paramyxoviridae

Members in the family are enveloped viruses with single stranded negative-sense RNA genome.Currently the family *Paramyxoviridae* has two subfamilies named *Paramyxovirinae* and *Pneumovirinae.*The former has five genera: respirovirus, morbillivirus, rubulavirus, henipavirus and avulavirus. The latter has two genera: pneumovirus and metapneumovirus. The members survive moderately well in the environment; all replicate in the upper respiratory tract epithelium and have a broad host range affecting farm and companion animals, birds and man. Some members also have cell tropism for reticuloendothelial, enteric and neural cells causing significant pathology and disease of the bowel and/or CNS. In dogs two members are significant pathogens. The viruses concerned are canine distemper virus (CDV) in genus morbillivirus and parainfluenzavirus-2 (PIV-2) in genus respirovirus. Both viruses are transmitted by aerosol which initiates primary infection in respiratory tract and/or tonsilar epithelium and dissemination throughout the bronchial tree. Two-5 days later respiratory disease may follow with signs of primary fever, dyspnoea, nasal discharge, inappetence. Progeny virus from primary CDV replication also initiates infection of macrophages and then of lymphocytes both of which disseminate the progeny virus to the epithelium and lymphoid tissue of small intestine giving rise to vomiting and diarrhoea and then anorexia. Other organs infected following macrophage-lymphocyte viraemia are neurones and brain macrophages and epithelia of endometrium. Significant infection at these sites may result in CNS disease and/or transplacental invasion of the foetus which may die. The CNS disease signs observed are ataxia, muscle tremors and paralysis and coma. PIV-2 has been associated with kennel cough. Severe disease results during combined infection with CDV or *Bordetella bronchiseptica*.

3.4. Rhabdoviridae

Rabies virus (RV) in genus lyssavirus of family *Rhabdoviridae* has long been the most feared zoonosis. All mammals are susceptible to RV. Viral particles are bacilliform and/or bullet-shaped, enveloped and contain one molecule of non-infectious, linear, negative-sense, single-stranded RNA. Common reservoir hosts are members of canids (fox, dog, wolf and jackal), mustelidae (skunk, polecat and some other species) and chiropetra (bats). RV transmission is usually by bite of infected animals shedding virus produced in salivary gland. Primary virus replication occurs in muscle fibres at the site of bite from where the progeny virus gains access into the nerve fibres and migrates along the axoplasm centripetally. Once in the neurone cell body virus replicates followed by centrifugal migration down the cranial nerves to the salivary gland where the virus replicates and is shed in saliva. RV occurs worldwide with the exception of countries which practice strict quarantine regulations. Rabies is an increasing threat to cats and dogs in endemic areas and the infection is almost always fatal after a paralytic and respiratory distress disease. In usual circumstances the only risk of rabies virus transmission is by the bite or scratch of a rabid animal, highly humid environment such as in bat caves the virus may be transmitted via

aerosols as well. The control of rabies in different regions of the world poses very different problems, depending on which reservoir hosts are present and the level of infection therein [9].

3.5. Retroviridae

The family name derives from members possessing reverse transcriptase enzyme (RT). The family is sub divided into 3 subfamilies: *Oncovirinae, Lentivirinae* and *Spumavirinae.* Members in the subfamily are further classified as genera, subgenera and species. Virus particles are enveloped covering an icosahedral capsid containing helical nucleocapsid. The genome comprises two copies of linear positive-sense, single-stranded RNA (+ssRNA) which is not infectious per se. The viral genome occurs as an inverted dimer held together at the 5′ end by hydrogen bonds possibly through base paring. Retrovirus replication is unique among +ssRNA viruses because they first convert +ssRNA to −DNA copy using the virion RT (RNA dependent DNA polymerase) and then a circular double-stranded (DS) DNA copy which is integrated into host cell chromosome by a second viral enzyme, a DNA ligase. The integrated DS DNA then codes for new +ssRNAs which then serve as new genomes or messenger RNAs. The later stage of viral replication is catalysed using cellular enzymes and organelles.

In companion animals Feline leukaemia virus (FeLV) in subfamily *Oncovirinae* and feline immunodeficiency virus (FIV) in subfamily *Lentivirinae* cause significant diseases in cats. However in dogs and rabbits retroviruses are not significant pathogens. FeLV is a leading killer of cats causing lymphosarcoma and leukaemia which are the most important and common tumours of cats. Cats become infected through close contact with other infected cats and ingestion of or contamination from licking of wounds by infectious saliva during mutual grooming. Virus replicates in oropharynx and/or leukocytes followed by viraemia due to infected leukocytes (B cells, monocytes and macrophages) which disseminate the virus to bone marrow, thymus, salivary glands and reproductive organs. In the majority of cats FeLV causes a self limiting infection. But in some 30% of infected cats a persistent infection remains depending on age. They remain non-viraemic with neutralising and Feline Oncovirus Membrane Associated (FOCMA) antibodies. They do not shed virus and do not develop leukaemia. However, in some cats, a persistent viremia is accompanied with high FOCMA specific antibodies. These cats develop neutralising antibodies and become healthy or the FOCMA antibodies decline and the cats develop leukaemia. Persistently infected cats are the source of disease spread. The virus is immune suppressive in those cats upon infection of T and B lymphocytes and myeloid cells. This is manifest as lymphoid or myeloid leukaemia with increased blood count of lymphoblasts or myeloblasts, respectively, and lymphosarcoma. On the other hand infection may also lead to severe immunodeficiency without lymphosarcoma development. Although the viral genome has been demonstrated in the tumours, the virus itself can be rarely isolated from such tumours. Generalised B cell tumours of lymph nodes (known as multicentric lymphosarcoma), thymic and alimentary lymphosarcomas have been observed in FeLV infected cats. In the thymic form there is marked T cell hyperplasia enlarging thymus which eventually fills most of the thoracic cavity causing dyspnoea. In the alimentary form B cell tumours develop in the wall of the intestine. These FeLV induced neoplasms may also result in haemolytic or hypoplastic anaemia, immunosuppression and reproductive failure. Infection of placenta followed by transplacental infection of foetus may result in foetal death.

FIV is found worldwide in domestic cats and wild felids namely snow leopards, lions, tigers, jaguars and bobcats. FIV infection in cats has three stages, just like HIV infection in humans. The initial acute stage is characterised by fever, swollen lymph nodes, oral,

respiratory, eye and intestinal symptoms which may be recurrent or chronic in occurrence. Affected cats may have nasal and eye discharge, cloudy cornea and diarrhoea. In the second latent stage, often lasting many years the immune system is slowly destroyed leading to immunodeficiency followed by the third AIDS-like stage. Feline immunodeficiency virus is shed mainly in the saliva and the principal mode of transmission is through bites. In this perspective free-roaming animals are at the greatest risk of infection and hence FIV is uncommon in closed catteries. Sexual contact does not appear to be a significant mode of transmission although the virus may be shed in semen. The virus is transmitted to kittens from acutely infected queens through colostrum and milk [9].

4. Emergent and potential virus diseases

An important event in companion animal viral disease ecology has been the jump by contemporary strains of equine influenza H3N8 virus (Orthomyxovirus) to racing dogs first recognised during an outbreak of respiratory disease in racing greyhounds at a kennel in Florida in January 2004 [84]. In this outbreak 8 greyhounds died of haemorrhagic pneumonia while 14 remaining dogs had a milder illness manifest initially as fever and then coughing for 10–14 days. A variety of tests including genetic sequence analysis and phylogenetic comparisons led to the conclusion that all three canine flu virus isolates from January 2004 outbreak had evolved from equine influenza H3N8 virus and formed a single phylogenetic cluster. The prototype strain was then named A/canine/Florida/43/2004 (canine/FL/04).These authors also concluded that the entire (all eight RNA segments) of the horse virus had been transmitted to the dog. This may have been neither the first nor the last episode of the disease. Tests on archival dog sera and lung tissue and dog sera collected in early 2005 from various states of USA indicate occurrence of canine H3N8 influenza virus prior to and after the 2004 outbreak [84]. These authors also provide evidence of the virus's transmissibility to pet dogs and the data suggest virus transmission by virus aerosol. Occurrence of an isolated case of canine H3N8 flu virus in the UK was identified by serology [85]. One important factor in interspecies transmission of any virus including influenza viruses is the presence of appropriate viral receptors in the respiratory tract epithelial cells of the novel host. The equine influenza haemagglutinin recognises α2,3 sialic acid linkages. Of concern would be if the new H3N8 dog flu virus became more widespread in dog populations and if it jumped to cats. The dog is also susceptible to highly pathogenic avian influenza (HPAI) virus of H5N1 subtype [86,87] and the virus was the cause of fatal dog infection in Thailand [88,86]. Suceptibility of dogs to HPAI H5N1 disease has been reproduced experimentally [87].

HPAI H5N1 virus has also jumped to domestic cats and wild felids and natural HPAI H5N1 virus infection was the cause of fatal disease in domestic cats and other large felids such as tigers and leopards in Thailand [89,90,86]. The susceptibility of domestic cats to HPAI H5N1 virus was also proven experimentally [91–93,87]. The availability of appropriate receptor(s) in the lower respiratory tract (LTR) of the novel host is an important prerequisite for the novel virus to initiate infection in the new host and cause viral pneumonia. Like the dog, cat LTR (and also human's) has terminal α2,3-Gal linkages in the LTR [94] which are the preferred ligands for H5N1 virus and apparently also for H3N8 influenza virus.

In view of the fact that two newly emergent paramyxoviruses in the new genus henipavirus namely Hendravirus and Nipahvirus have jumped species from reservoir petropid fruit bats to man, horses and pigs in Australia and the Far East causing fatalities in all three unnatural hosts [95,96] it is important to be aware of experimental studies showing susceptibility of domestic cats

to these new important pathogens. Transmission of both henipaviruses to cats is possible since infected horses and pigs shed virus oronasally [97,98]. Experimentally cats were susceptible to Hendravirus by subcutaneous, intranasal, oral inoculation and also to in contact transmission resulting in severe interstitial pneumonia, generalised thrombosis and necrosis of small blood vessels and necrotic lesions in lungs, intestine, liver and kidneys; infected cats shed virus in secretions of oropharynx and urine [99]. Oronasal inoculation of cats with a human isolate of Nipahvirus resulted in febrile respiratory and neurological disease in cats which also incurred vasculatis and haemorrhages in lymph nodes, trachea, lung and pulmonary infarcts.

Another potential cat pathogen is West Nile virus (WNV). WNV is mosquito-transmitted flavivirus belonging to the Japanese encephalitis (JE) serocomplex of the family *Flaviviridae* [100]. All members of the JE complex are transmitted by mosquitoes. Bird-feeding mosquitoes are the principal vectors of WNV. WNV has been isolated from 43 mosquitoe species mainly of the genus Culex [101]. High long-term viraemia, sufficient to infect vector mosquitoes is required for field transmission of WNV. The latter occurs in infected birds which are the principal reservoir hosts of WNV whereas mammals are less important. Bird-mosquitoe cycle in wetlands is the common mode of WNV transmission but bird-tick cycle in certain dry and warm habitats also occurs [101]. Importantly for this paper WNV naturally infects dogs [102–105], cats [104]. Susceptibility of dogs and cats to WNV has also been investigated experimentally [106]. Strains of WNV vary significantly in virulence for mammalian and avian species [107–109]. The insect bite results in viraemia and visceral viral replication which produces secondary viraemia which could lead to CNS infection. The visceral viral replication may cause fever, depression anorexia and some mortality while CNS replication may result in encephalitis and neurological signs such as tremors, ataxia and death [110,108,111]. Infected dogs and cats may undergo this pattern of disease pathogenesis although it is very rare for cats and dogs to be infected in the wild.

5. Immunoprophylaxis

As described earlier, vaccines are available for many years against the common well known diseases. For dog viral (and bacterial) diseases, vaccines offered by the major companies are against CDV, CAV-1 and 2, CPV, CPI-2 and rabies and some companies also for CCoV and one for CHV-1 in various combinations. For the cat vaccines are available against diseases caused by FPLV, FCV, FHV-1, FeLV, FCoV, FIPV, FIV and rabies virus. Vaccines from the companies are broadly similar in formulation and presentations (Tables 1 and 2) but vary with respect to the number of components. Furthermore, it is important to point out that some vaccine components consist of live antigens whereas others of killed. The choice between live and killed depends largely on the immunological response which is to be induced and the immunological background of the target animal (presence of maternal derived antibodies, age at which the animal is supposed to be immune, etc.) Tables 1 and 2 represent the licensures in the UK, but it should be noted here that in other countries, not all or other formulations may be licensed due to national or economic reasons. Viral vaccines are sometimes dissolved in solvents containing bacterial components such as the *Leptospira* spp. and *Bordetella brochispetica* antigens. In the UK, for the dog viruses the number of products ranges from 3 (Pfizer) to as many as 8 (Schering-Plough, S-P). Most companies have 5–6 products, mostly as polyvalent (multi-disease) vaccines. For the cat, the products range is 2 (S-P, Virbac), 4 (Intervet), to 6 (F-D, Merial). The reason for the multiple product range is likely to be the vaccine duration of immunity (DOI) varying from 1 year or

Table 1
Canine viral disease vaccines.

Company and trade name	Vaccine	Presentation	Handling and claims
FORT DODGE Duramune Range	1. PPI + L	V. LFD CPV (SAH) + CPI-5 V. K-L.	Reconstitute V. LFD with K-L and apply S/C from 6 to 10 weeks and again 3–4 weeks later. OI: from 2 weeks DOI: 1 year; CPI-5 unknown. Contra-indicated for pregnant bitches.
	2. PPI + LC	V. LFD: CPV (SAH) + CPI-5 (FDL) and V. K-L + K-CCoV (TN449).	As with PPI + L. OI: From 2 weeks. DOI: 1 year; CPI-5 unknown. Contra-indicated for pregnant bitches.
	3. DAPPI + L	V. LFD: CDV (Ondersteport) + CAV-2 (V197) + CPV (SAH) + CPI-5 (FDL) and V. K-L.	As with PPI + L. OI: From 2 weeks. DOI: 3 years for CDV, CAV and CPV but CPI-5 unknown. Contra-indicated for pregnant bitches.
	4. DAPPI + LC	Same live viruses as 3 and V.-K + K-CCoV (TN449).	As with PPI + L. OI: From 2 weeks. DOI: 1 year for all antigens except CPI-5. Contra-indicated for pregnant and lactating bitches.
	5. PPI + LC	Same live viruses as 1 and V. K-L + K-CCoV (TN449).	As with PPI + L. OI: From 2 weeks. DOI: 1 year for all antigens but CPI-5 unknown.
	6. Puppy DP + C	V. LFD: CDV (Ondersteport) + CPV (SAH) and V. K-CCoV (TN449) and solvent.	Reconstitute V. LFD with solvent and apply S/C from 6 to 10 weeks and again 2–4 weeks later. OI: from 2 weeks. DOI: 1 year. Contra-indicated for pregnant and lactating bitches.
INTERVET Nobivac Range	1. DHP	V. LFD: CDV (Ondersteport) + CAV-2 (Manhattan LPV3) + CPV (154^3) and solvent.	Reconstitute V. LFD with solvent or Nobivac Lepto2 or Nobivac Rabies and apply S/C from 6 weeks and again at 10 weeks. OI: 1 week (CDV and CPV) 2 weeks (CAV). DOI: 3 years.
	2. DHPPI	Same as DHP + live CPI-5 and solvent.	As with DHP vaccine. OI: 1 week (CDV, CPV and CAV) and 4 weeks (CPI-5). DOI: 3 years (CDV, CPV and CAV); CPI-5 unknown.
	3. Parvo-C	V. LFD CPV and solvent.	Reconstitute as per DHP vaccine and apply S/C from 4 weeks and booster at 10 weeks but a single dose for puppies 10 weeks and older. OI: 1 week. DOI: 3 years.
	4. PI	V. LFD CPI-5 (Cornell) and solvent.	Reconstitute as per DHP Vaccine and apply S/C from 8 weeks and booster 2–4 weeks later. OI: 4 weeks. DOI: unknown.
	5. Rabies	V. K-Rabies (pasteur RIV) + Al (OH) adjuvant.	Apply S/C to dogs and cats from 4 weeks when puppies should be boosted at 3 months. OI: 2–3 weeks. DOI: 3 years.
MERIAL Eurican Range	1. Herpes 205	V. K-CHV-1 (F205) gB glycoprotein (0.3–1.75 μg) in oil adjuvant.	Apply S/C near or soon after mating and again 1–2 weeks before whelping and similarly at or during each pregnancy.
	2. DHPPI	V. LFD: CDV + CAV + CPV + CPI-2.	Reconstitute with Eurican L vaccine and apply S/C from 8 weeks and boost 3–5 weeks later and then annually.
	3. L	V. K-L	As with DHPPI. OI: 2 weeks. DOI: 1 year.
	4. P	V. LFD: CPV.	As with DHPPI but single injection for dogs 12 weeks and older. OI: 1 week. DOI: 1 year.
	5. Rabisin	V. K-Rabies with Al (OH) adjuvant.	Apply S/C to dogs and cats from 3 months and boost every 2 years.
PFIZER Vangard Range	1. 7	V. LFD: CDV (Synder Hill) + CAV-2 (Manhattan) + CPI-5 (NL) V. LS: CPV (NL-35-D) + K-L.	Reconstitute V. LFD with V. LS + K-L and apply S/C twice 2 weeks apart to puppies 10 weeks and younger but single dose for older dogs OI: 2 weeks. DOI: 1 year (also for CAV-1) but unknown for CPI-5. Contra-indicated for pregnant bitches.
	CPV	V. LS CPV (NL35-D).	As per Vangard 7. OI: 2 weeks. DOI: 1 year. Contra-indicated for pregnant bitches.
	CPV-L	V. LS CPV (NL35-D) + K-L	As per Vangard 7. Same claims as CPV vaccine. Contra-indicated for pregnant bitches.
SCHERING–PLOUGH Procyon & Quantum Range	1. Dog DA$_2$PPI/CVL	V. LFD: CDV (Distemperoid) + CAV-2 (Ditchfield) + CPV (SAH 2b) + CPI (Philips Roxane) V. K-CCoV (FEC-SAH) + K-L.	Reconstitute V. LFD with V. K-CC+ K-L and apply S/C or I/M from 6 weeks and boost 3–4 weeks later. OI: 3–4 weeks. DOI: 3 years for CDV, CAV (1 and 2) and CPV; 1 year for CPI, CCoV and Lepto serovars.
	2. Dog DA$_2$PPI/L	Same as DA$_2$PPI/CVL but without CCoV.	Same as DA$_2$PPI/CVL vaccine for the components present including claims.
	3. Dog PI/CVL	V. LFD: CPI (Philips Roxane) V. K-CCoV (FEC SAH) + K-L (115 and 117).	Reconstitute as vaccines 1 and 2. Same claims for the active components present in DA$_2$PPI/CVL.
	4. Dog PI/L	Same as vaccine 3 but without CCoV antigen.	Reconstitute and apply as vaccine 1. Same claims for the components present in vaccine 1.
	5. Dog 7	V. LFD: CDV + CAV-2 + CPI-2 V. LS CPV + K-L.	Reconstitute V. LFD with V. LS CPV + K-L + and apply S/C twice from 10 weeks and again at 12 weeks but a single dose to older puppies and then annually.
	6. Dog CPV	V. LS CPV.	Apply S/C from 6 weeks and again at 12 weeks and then annually. There are other options.
	7. Dog CPV-L	V. LS CPV + K-L.	Apply as per Quantum CPV.
	8. Rabies	V. K-Rabies (Flury) suspension with Al (OH) Adjuvant.	Apply S/C to dogs and cats from 3 months and then every 3 years.
VIRBAC Canigen Range	1. DHP	V. LFD CDV (Ondersteport) + CAV-2 (Manhatan) + CPV (154^3) and solvent.	Reconstitute V. LFD with solvent or Canigen Lepto 2 or Canigen Rabies and apply S/C from 6 weeks and again at 12 weeks. OI: 1 week for CDV and CPV and 2 weeks. DOI: 3 years when booster recommended.

Table 1 (*Continued*)

Company and trade name	Vaccine	Presentation	Handling and claims
2. DHPPI	V. LFD: CDV + CAV-2 + CPV + CPI and solvent.	Reconstitute V. LFD with Canigen Lepto 2 or solvent and apply S/C from 6 weeks and again 4 weeks later. Additional dose of Canigen PI recommended at 8 weeks. DOI: 3 years for CDV, CPV and CAV and 1 year for CPI when booster recommended. Not recommended for ferret and mink.	
3. PI	V. LFD: CPI and solvent.	V. LFD: CPI and solvent.	Reconstitute V. LFD with solvent or Canigen Lepto 2 or Canigen Rabies and apply S/C from 8 weeks and again 2–4 weeks later but a single dose 12 weeks onwards and then annual booster. OI: 4 weeks. DOI: 1 year.
4. Rabies		V. K-Rabies (Pasteur RIV) + aluminium phosphate adjuvant.	Apply S/C or I/M to dogs and cats from 3 months and then every 3 years. OI: 2–3 weeks. DOI: 3 years.

Vaccines are sold in the UK. It is therefore possible, dependent on licensing authorisation sought by the companies, that there is variation in products and product composition available in other countries. Tables are merely a guide to actual formulations that are possible.
Abbreviations: V. = vial of; LFD = live freeze dried pellet of viruses; LS = live suspension of; K = inactivated, as liquid suspension or emulsion of; S = suspension; L = mixture of Leptospira serovars canicola and icterohaemorrhagiae; + = combined with; OI = onset of immunity in weeks after the primary course of vaccination; DOI = duration of immunity in years; MDA = maternally derived antibody to antigen(s); S/C = subcutaneous; I/M = intramuscular. See text for abbreviated virus names.

less (CPI-2, FeLV) to 3 years (CDV, CAV-2, CPV and rabies virus); for most diseases one vaccine formulation would protect against diseases ranges from 5 to 8 and 2 to 5 for the dog and cat viral and bacterial diseases, respectively. It should be noted that not all companies claim DOI of 3 years for CPV disease. Also noteworthy is the fact that most, with an odd exception, of these vaccines were derived by conventional attenuation and/or inactivation processes in tissue culture some 10–20 years ago. The tissue culture technologies have been much refined to aid the production, quality (purity and control) and improved yield of active components. Another important point to mention is that these various vaccines contain different viral strains and their efficacy was assessed using different challenges (virus strains, inocula, animals) and sample analysis was using different tests. This clearly does not allow an objective analysis of their relative efficacy. Because of the age of these vaccines and the recent emergence of virulent variants of some viruses notably CPV (the 2a, 2b and 2c variants) and FCV (VS-FCV) [22,23,112] and the new respiratory coronavirus (see above for references) the need for assessment of efficacy of these now old vaccines against the newly emergent viruses is clearly necessary but would be costly. There are only limited investigations on this subject. An exception, to our knowledge, is the recent controlled study in susceptible dogs for CPV 2 component in Nobivac DHPPi (Table 1) against CPV 2c oral challenge which showed that the vaccine was fully cross protective [113]. Published information on the prevalence and the incidence of disease due to the recently recognised group 2 respiratory coronavirus [65] is limited but this could be another pathogen for which immunoprophylaxis may be needed. Domestic and scavenging dogs are a significant source of human rabies worldwide and vaccination of dogs has been highly beneficial in this respect [114]. CDV is a cause of fatal disease in many species of carnivores. CDV related viruses have been identified in seals (phocid distemper virus), dolphins, whales and porpoises [115,116], and vaccination strategies have shown some success [117]. CDV transmitted by domestic dogs was associated with fatal neurological disease in lions in Serengeti National Park in Tanzania and dog vaccination against CDV in affected areas was beneficial [118]. Although currently available live CDV vaccines are suitable for immunising domestic dogs and farmed mink. A CDV

vaccine based on the Onsterstepoort strain is safe and efficacious in Lions by eliciting a protective neutralising antibody response [119]. The same vaccine has been used effectively in otters and seals (showing vaccine efficacy in the face of Phocine distemper outbreak (Intervet/Schering-Plough, unpublished). The live vaccine safety concern and the global CDV distribution involving a wide variety of susceptible species, require new safe vaccines for the protection of wild species as well as eradication or reduction of CDV from wildlife [115]. A further requirement is strategies for wildlife vaccination as has been used for rabies and anticipated for RHDV and MV diseases of wild rabbits (see below).

Although canine H3N8 flu virus disease is quite new, plans for vaccine against it were afoot soon after the outbreak of the fatal respiratory disease [84]. These authors were working towards a vaccine for this new dog disease (personal communication by Dr. Cyanda Crawford to Allison Clark [120]. That there is commercial interest in canine H3N8 flu virus vaccine is indicated by a recent controlled efficacy study in dogs with two experimental canarypoxvirus-H3 subtypes (from two strains) live recombinant vaccine [121]. This study was a joint effort by Merial, Sanofi Pasteur and Cornell University.

For the cat there are FCV vaccines from several companies (Table 2) but their efficacy against the newly emergent VS-FCV [35,112] remains unknown. The development of vaccines against FIP coronavirus (FIPV) has proved cumbersome and consequently there is only one (Pfizer's, not in Table 2) live intranasal temperature sensitive (TS) vaccine licensed in some countries [122,123]. However efficacy of this TS FIPV vaccine is a matter of debate [124,125]. A promising experimental oronasal live FIPV vaccine lacking group-specific gene cluster 3abc, derived by site directed mutagenesis of a virulent lethal FIPV strain was an innocuous efficacious vaccine [126]. Clearly there is a way to derive an effective FIPV vaccine. The observation that cats can recover naturally from FeLV infection led to development of vaccines (see Table 2). These however are not fully protective [127–129]. Thus there is an ongoing effort to develop improved effective FeLV vaccines. The target is for a vaccine that would prevent establishment of both viraemia and latent bone marrow infection. The approaches investigated have been vaccinia-FeLV [130], canarypox-FeLV [131] and FHV-1-FeLV [132] live vector

Table 2
Feline viral disease vaccines.

Company and trade name	Vaccine	Presentation	Handling and claims
FORT DODGE Fevaxyn & Katavac Range	1. FELV	V. K-FELV (A7B) + adjuvant.	Apply twice S/C 3–4 weeks apart from 9 weeks and boost annually. Can be used to reconstitute Katavac CHP.
	2. ICHP	V. K-FPLV + FHV-1 + FCV + mineral oil adjuvant.	Apply twice S/C 3–4 weeks apart from 8 weeks and then annually.
	3. ICHPCHLAM	V. K-FPLV + FHV-1 + FCV + Chlamydophila psittaci + mineral oil adjuvant.	As ICHP from 8 weeks.
	4. PENTOFEL	V. K-FPLV + FHV-1 + FCV + Chlamydophila psittaci + FeLV + adjuvant (Ethylene/maleic anhydride + neocryl XK-62 + emulsigen SA).	As ICHP from 9 weeks.
	5. KATAVAC CHP	V. LFD: FCV + FHV-1 + FPLV and solvent.	Reconstitute V. LFD in solvent or Fevaxyn FELV and apply S/C to kittens from 9 weeks but once to cats 12 weeks and older.
	6. KATAVAC ECLIPSE	V. LFD: FCV + FHV-1 + FPLV V. Fevaxyn FeLV.	Reconstitute V. LFD with V.K-FeLV and apply twice S/C 3–4 weeks apart from 9 weeks and boost annually.
INTERVET Nobi-vac Range	1. DUCAT'	V.LFD: FHV-1 (G2620A) + FCV (F9) and solvent.	Reconstitute V. LFD with solvent or Nobivac Rabies (Table 1) and apply S/C to cats from 8 weeks onwards and again 3–4 weeks later and boost annually.
	2. FELV	V. Subunit p45 FeLV envelope + Al (OH) and Quil A.	Apply S/C or I/M twice from 9 weeks onwards 3 weeks apart and boost annually. OI: 3–4 weeks.
	3. FORCAT	V. LFD: FHV-1 (G2620A) + FCV (F9) + FPLV (MW-1) + Chlamydophila felis (Baker).	Reconstitute V. LFD with Nobivac FELV or Rabies or solvent and apply S/C twice 3–4 weeks apart 9 weeks onwards and boost annually. OI: 3–4 weeks. DOI: 1 year (FHV-1, FCV and C. Felis) and 3 years (FPLV).
	4. TRICAT	V. LFD: FHV-1 + FCV + FPLV and solvent.	As with FORCAT. O I: 1 week (all antigens).
MERIAL Purevax Range	1. FELV	V. Suspension of live Canarypox (vCP97)-FeLV recombinant and solvent.	Apply S/C twice 3–5 weeks apart from 8 weeks and boost annually. Contra-indicated for pregnant animals but indicated for lactating cats.
	2. RC	V. LFD: FHV-1 (F2) + K-FCV (431 and G1) and solvent.	As with FELV. For high levels of MDA delay vaccination to 12 weeks and primary course booster 3–4 weeks later.
	3. RCP	V. LFD: FHV-1 (F2) + FPLV (PLIIV) + K-FCV (431 and G1) and solvent.	As with RC.
	4. RCPCH	V. LFD: FHV-1 (F2) + FPLV (PLIIV) + C. felis (905) and solvent.	As with RCP from 8 weeks.
	5. RCPCHFELV	V.LFD: FHV-1 (F2) + FPLV + C. felis (905) + Canarypox-FeLV + K-FCV (431 and G1) solvent.	As with RC or RCP.
	6. RCPFELV	V. LFD FHV-1 (F2) + FPLV (PLIIV) + Canarypox (vCP97)-FeLV recombinant + K-FCV (431 and G1) and solvent.	As with RC or RCP.
Pfizer Felocell	1. CVR	V. LFD: FPLV (snow leopard strain) + FHV-1 (FVRm) + FCV (F9) and solvent.	Reconstitute V. LFD with solvent and apply S/C twice 3–4 weeks apart from 9 weeks and boost annually. Contra-indicated for pregnant queens.
SCHERING-PLOUGH Quantum Range	Cat CVRP	V. LFD FCV + FHV-1 + FPLV and solvent.	Reconstitute V. LFD with solvent or Quantum cat FELV and apply S/C twice 3–4 weeks apart from 9 weeks and boost annually. Contra-indicated for pregnant cats. OI: 3 weeks. DOI: 1 year.
	Cat FELV	Suspension of subunit FeLV glycoprotein 70 and FOCMA antigens + adjuvant.	As with Quantum CVRP but safe for pregnant cats. OI: 3 weeks. DOI: 1 year.
VIRBAC	1. Feligen RCP	V. LFD: FPLV (DSV LR 72) + FHV-1 (F2) + FCV (F9) and solvent.	Reconstitute V. LFD with solvent or Leucogen and apply twice S/C from 9 weeks and again 2 weeks later and then annually. Contra-indicated in pregnancy.
	2. Leucogen	V. p45 FeLV envelope antigen expressed in E. coli + Al (OH) and Quil A as adjuvants.	Apply S/C or I/M twice from 9 weeks and again 2–3 weeks later and then annually. Recommended for queens prior to mating.

See Table 1 text for rabies virus vaccine for immunising cats. See legend of Table 1.

vaccines. The vaccinia-FeLV vaccine was ineffective while the other two live vector vaccines were not better than existing vaccines. However, experimental vaccines that showed excellent protection were the FeLV iscoms [133] and FeLV DNA co-administered with interleukin 12 (IL-12) and IL-18 cytokine genes [134].

FIV is a cause of significant disease in domestic cats worldwide. Immunoprophylaxis for FIV disease is limited and only one company (F-D) offers a vaccine, approved in spring 2002. Currently the use of the vaccine is not recommended by The American Association of Feline Practitioners. Like its human counterpart, the

Table 3
Rabbit and Pigeon viral disease vaccines.

Company and trade name	Vaccine	Presentation	Handling and claims
Vaccines for rabbits			
CEVA	Lapinject VHD	V. K-RDDV (P174) + oil adjuvant.	Apply S/C from 5 weeks and boost annually. OI: 6 days. DOI: 1 year. Safe for pregnant rabbits.
FORT DODGE	Cylap	V. K-RHDV + oil adjuvant.	Apply twice S/C from 2.5 to 3 months and 4 weeks later and then annually. Safe for pregnant rabbits.
INTERVET Nobivac	Myxo	V. LFD: Shope fibroma virus and solvent.	Reconstitute V. LFD with solvent and virus and solvent and apply intra dermally or S/C from 6 weeks and older rabbits. OI: 2 weeks and DOI: 6 months. Contra-indicated for breeding and pregnant rabbits.
Vaccines for pigeons			
FORT DODGE Colombovac Range	1. PMV	V. K-PMV-1 + adjuvant.	Apply S/C to racing and show pigeons from 3 weeks and then annually. Adult birds can be similarly vaccinated.
	2. PMV/POX	V. LFD PPV V. K-PMV-1 + adjuvant.	Reconstitute V.LFD PPV with V. K-PMV-1 and apply S/C to racing and show pigeons from 6 weeks and then annually. Adult birds can be similarly vaccinated.
INTERVET	NOBILIS PARAMYXO	V. K-PMV-1 + mineral oil adjuvant.	Apply S/C from 6 weeks before race or exhibition and then annually. OI: 4 weeks. DOI: 1 year.

See legend of Table 1.

immunodeficiency virus of human AIDS, FIV presents a formidable challenge for vaccine development despite a vigorous host immune response to the virus. Various approaches for a vaccine have been investigated [135] with some success. It has been shown that a multi-epitopic vaccine for instance does induce an immune response which is not protective [136]. An important difficulty has been the strain specificity of vaccines in that experimental vaccines were not protective for heterologous strains [137]. The newly emergent HPAI H5N1 induced viral disease in dogs and cats is clearly a new challenge for the institutional and industrial virologists to develop yet another vaccine. In this regard a conventional killed adjuvanted H5N6 flu virus vaccine was protective against lethal HPAI H5N1 experimental challenge in a controlled efficacy study in cats [93].

Booster vaccination after the primary course and DOI is an important issue in the recent vaccination debate particularly for the dog and cat vaccines. However, the time for the booster vaccination is difficult to assess since (i) response of individual animals to routine vaccination is highly variable which is also influenced by the level of MDA at primary vaccination, (ii) the frequency of field exposure is often unknown and (iii) products vary with respect to potency and formulation. Antibody test may be appropriate for establishing residual immunity for some antigens but not all and the cost is likely to exceed that of booster vaccination [138]. However, in general, for the so-called core dog vaccines for CAV-2, CDV, CPV and rabies and cat vaccines for FPLV, FCV, FHV-1 and rabies published data suggest a minimum DOI of 3 years [139]. Therefore for these core vaccines a general vaccination guideline should be first vaccination at as early as 6 weeks of age or older (>12 weeks) depending on disease and available vaccine type (live versus killed), then again at 1 year and then every 3 years. For the non-core vaccines yearly boosters are recommended. Animals with high MDA may require two vaccinations in the primary vaccination regimes.

For rabbits, diseases covered by vaccine companies are those due to RHDV and MV but the choice of vaccines is rather limited (Table 3). For RHDV CEVA and F-D have a similar formulation of rabbit grown liver antigen [140,141] plus oil adjuvant. Since

RHDV has failed to grow in tissue culture, various expression vectors have been developed for the production of RHDV capsid VP60 protein. These vectors comprise E. Coli [142], Saccharomyces cerevisae [143], poxviruses: myxoma [144], vaccinia [145], canarypox [146]. VP60 was also produced in rabbit kidney cell line RK-13 [147] and potato [148] and baculovirus [149]. Many of the vector expressed VP60 antigens incorporated into experimental vaccines were immunogenic and protective for rabbits against fatal RHDV challenge [150]. Commercially only one MV disease for domestic rabbits is marketed by Intervet (Table 3). The latter is a live heterotypic vaccine based on less pathogenic leporipox Shope fibroma virus. For both RHDV and MV diseases a key requirement is vaccines which could be used for both domestic and wild rabbits. The latter play an important ecological role in Mediterranean and other ecosystems. This entails a strategy for wildlife immunisation which is feasible as has been achieved for sylvatic rabies control in Europe and North America by oral vaccines delivered by baiting [151–153]. Other methods are delivery by biting insects and/or by direct horizontal animal to animal vaccine spread. All these three modes of vaccination against RHDV and MV diseases were elegantly demonstrated by controlled experimental challenge studies [150]. However we do wonder if such a vaccine would indeed be commercialised.

6. Conclusions

The main conclusions we draw from the above account of important viral diseases of cats, dogs and rabbits are:

1. Viruses from several different families naturally infect these companion animals and cause significant disease. Most of the viruses are transmitted via the oropharyngeal route by virus shed in secretions of saliva, nasal mucus, aerosol and/or faeces. Virus in secretions is inhaled and/or ingested and initiates primary replication in mucosa of the respiratory and/or intestinal tracts; rabies virus shed in saliva, is however delivered to myocytes, the site of primary replication, via bite while myxomavirus is trans-

mitted by blood feeding arthropod vectors such as mosquitoes, fleas and others in addition to inhalation of virus.

2. In disease pathogenesis an important determinant for significant disease is if the virus is able to infect leukocytes and then be disseminated to internal organs for secondary replication and cause pathology. However most cat and dog coronaviruses are generally restricted to the primary site of infection and cause acute, self-limiting mild enteric or respiratory and disease. Vicerotropic virulent strains also occur naturally with variable frequency following mutational changes. Examples are FCoVs causing infectious peritonitis and the recent cases of genotype 2 CCoV strain CB/05 disease in dogs. Like the coronaviruses, most calicivirus infections of cats are limited to the respiratory tract resulting in self-limiting disease but recent emergence of vicerotropic VS-FCV variants cause severe disease in cats and the disease pathogenesis has similarities to the usually fatal disease of rabbits due to RHDV. Leukocyte-associated viraemia is also important in parvovirus disease of cats and dogs and related wild felids and canids.

3. The tropism for enteric epithelium and virus survival in faces has been important in evolution of the carnivore parvoviruses. CPV has naturally evolved relatively rapidly and the small evolutionary changes have been in virus capsid VP2 gene and interestingly were associated with the loss and then renovation of the feline host range.

4. For the established viruses of the cats and dogs there is a good choice of vaccines developed 10–20 years ago. Hence, they are due for re-assessment for their efficacy for some components notably the newly emergent CPVs and VS-FCV. There is however the need for improved vaccines for FIPV, FeLV and FIV. This is also the case for MV and RHDV vaccines for rabbits. Also needed is RHDV vaccine for wild rabbits.

5. The recent emergence of HPAI H5N1 disease in cats and other large felids and that of H3N8 equine influenza virus in dogs are significant developments and may require vaccines should the viruses get established in these novel hosts and spread more widely. Also we should be aware that cats and dogs have the potential to acquire new viral diseases for example those due henipa paramyxoviruses.

Acknowledgements

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