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Review article

Feline herpesvirus

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Abstract – Feline herpesvirus (FHV-1; felid herpesvirus 1 (FeHV-1)) is an alphaherpesvirus of cats closely related to canine herpesvirus-1 and phocine herpesvirus-1. There is only one serotype of the virus and it is relatively homogenous genetically. FeHV-1 is an important cause of acute upper respiratory tract and ocular disease in cats. In addition, its role in more chronic ocular disease and skin lesions is increasingly being recognised. Epidemiologically, FeHV-1 behaves as a typical alphaherpesvirus whereby clinically recovered cats become latently infected carriers which undergo periodic episodes of virus reactivation, particularly after a stress. The primary site of latency is the trigeminal ganglion. Conventional inactivated and modified-live vaccines are available and protect reasonably well against disease but not infection, although viral shedding may be reduced. Genetically engineered vaccines have also been developed, both for FeHV-1 and as vector vaccines for other pathogens, but none is as yet marketed.

feline herpesvirus / pathogenesis / epidemiology / review

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1. AETIOLOGY

Feline herpesvirus 1 (FHV-1; felid herpesvirus 1 (FeHV-1)) is a member of the *Varicellovirus* genus of the herpesvirus subfamily *Alphaherpesvirinae* [17]. As well as domestic cats, FeHV-1 infects several other members of the Felidae [16, 25, 54, 91, 101, 103, 121, 135, 140]. The virus is closely related genetically and antigenically to canine herpesvirus-1 (CHV-1) and phocine (seal) herpesvirus-1 (PhV-1), and cross-protection between feline and PhV-1 has been reported [46–48, 71, 85–87, 153, 154]. A herpesvirus similar to FeHV-1, but distinct from CHV-1 has been isolated from dogs but the significance of this is unclear [24, 67].

All isolates of FeHV-1 appear to be relatively similar. Most produce a relatively uniform disease although some show reduced or increased virulence [39, 42]. Antigenically all isolates belong to one serotype, and they are relatively homogeneous on restriction enzyme analysis of their DNA [41, 52]. Some minor genetic differences have been reported for some strains, including differences in *Mlu 1* cleavage patterns, re-arrangements in the gC gene, and differences in the *Sal 1* site in the UL 17 herpes simplex virus gene homologue [43, 44, 59, 76]. Despite this, there is currently no useful method to study the role of individual FeHV-1 isolates in disease.

Like other herpesviruses, FeHV-1 contains double-stranded DNA and has a glycoprotein-lipid envelope. It is therefore relatively fragile in the external environment and is highly susceptible to the effects of common disinfectants [22, 117]. It can survive for only up to 18 h in a damp environment, less in dry conditions, and is also relatively unstable as an aerosol [20, 105].

2. PATHOGENESIS

The natural routes of infection for FeHV-1 are via the nasal, oral, and conjunctival mucous membranes, though experimentally other routes have been investigated. In pregnant queens for example, intravaginal instillation of virus has led to vaginitis and congenitally infected kittens [5] and intravenous inoculation has led to transplacental infection and abortion [58]. However, unlike some other alphaherpesvirus infections, under natural conditions abortion does not generally seem to occur [53], and reproductive disease in general does not seem to be a feature of FeHV-1 infection. Because of the increasing recognition that FeHV-1 may be involved in both acute and chronic ocular disease, the corneal route of infection has also been investigated experimentally [93].

Following infection, virus replication in the acute phase takes place predominantly in the mucosae of the nasal septum, turbinates, nasopharynx, and tonsils; other tissues including conjunctivae, mandibular lymph nodes and upper trachea are also often involved [32, 56]. Infectious virus can be detected in oropharyngeal and nasal swabs as early as 24 h after infection and generally persists for 1 to 3 weeks, although viral DNA may be detected by PCR for longer [141, 146].

Viraemia appears to be rare probably because, like some other respiratory herpesviruses, viral replication may be restricted to areas of lower body temperature like the respiratory tract. However, viraemia has occasionally been reported [56] when virus appears to be associated with peripheral blood leucocytes [134], and generalized disease may be seen particularly in debilitated animals or in neonatal kittens [119, 122, 139].

Infection of the respiratory epithelium leads to areas of multifocal epithelial necrosis with neutrophilic infiltration and fibrin exudation [14, 15, 39, 56, 108]; intranuclear inclusion bodies may be seen. Viral damage can also lead to osteolytic changes in the turbinate bones. A predilection of the virus for regions of

skeletal growth, including the turbinates, has been shown experimentally following intravenous inoculation of young kittens [57]. Lesions normally take between 2 and 3 weeks to resolve, although bone damage to the turbinates may be permanent. Primary lung involvement may occur but is rare [74].

The disease is not dependent on the presence of other microbial flora, as it has been reproduced experimentally in germfree cats [56]. However, secondary bacterial infection may enhance the effect of the virus and may lead to bacterial pneumonia, or chronic rhinitis, sinusitis or conjunctivitis [39]. The role of FeHV-1 itself in chronic rhinosinusitis is not clear: a recent study in a small series of cats found no difference in the proportion of cases and controls in which FeHV-1 DNA was detected using PCR [61]. However, interestingly, the turbinates are the earliest site of viral replication during reactivation [32], and FeHV-1 transcription is associated with an increase in nasal cytokine gene transcription, suggesting a role for FeHV-1 in nasal inflammation [62].

As with other alphaherpesviruses, latency occurs following the acute phase of disease, with periodic viral reactivation which is sometimes associated with recrudescence of clinical signs [39]. Latent infection has been demonstrated in trigeminal ganglia, using extended culture techniques such as explant or organ culture [35, 94]. FeHV-1 DNA, indicative of the presence of viral genome, has also been detected in trigeminal ganglia and in some other sites by PCR [111, 130, 146]. However, detection of latency associated transcripts (LATs) is probably the most accurate way to determine whether the virus is truly in a latent state: such transcripts, produced from the complementary strand to the immediate early gene(s), are expressed in relative abundance compared to other genes by alphaherpesviruses during latency. In FeHV-1, LATs have been detected in trigeminal ganglia by in situ hybridization [98] and more recently by detection of mRNA by RT-PCR [137]. In view of the increasing evidence that FeHV-1 may be involved in chronic ocular disease, and because of possible parallels with herpes simplex virus, the latter study [137] also examined corneas. However, although FeHV- 1 DNA was detected by PCR in both trigeminal ganglia and corneas, LAT transcripts were detected only in trigeminal ganglia suggesting true latency does not occur in the feline cornea.

Taken together, these data strongly suggest the main site of viral latency in FeHV-1 is the trigeminal ganglia. However, viral DNA has also been detected by PCR in other neurological sites (including olfactory bulb, optic nerve and cerebrum), and also in various ocular and respiratory tissues (including nasal turbinates and cornea, and less consistently, oral fauces, conjunctivae, lacrimal and salivary glands, tonsils and submandibular lymph nodes) [28, 111, 146]. Whether FeHV-1 is truly latent in such tissues, or whether low grade viral reactivation is being detected is not clear. Further studies of gene transcription and expression in putatively latently infected tissues would be required to determine this.

3. EPIDEMIOLOGY

FeHV-1 is shed in ocular, nasal, and oral secretions and transmission is largely by direct contact with an infected cat. Acutely infected animals are clearly one of the most important sources of virus, but latently infected carrier cats may also shed virus and infect susceptible cats [34]. There is no evidence of natural in utero transmission and there are no known non-feline reservoir or alternative hosts. In some situations, particularly within a cattery, indirect transmission may also occur through contamination of housing, feeding and cleaning

utensils, and personnel. However, because FeHV-1 is relatively short-lived outside the cat, the environment is usually not a long-term source of infection. Aerosols are not thought to be of major importance for the spread of FeHV-1: cats do not appear to produce an infectious aerosol for these agents during normal respiration, although sneezed macrodroplets may transmit infection over a distance of 1–2 m [34, 105].

As with other alphaherpesviruses, virtually all recovered cats become latently infected carriers, with intermittent episodes of detectable virus shedding (reactivation) occurring particularly after periods of stress. During such episodes infectious virus is present in oronasal and conjunctival secretions, acting as a source of infection to other cats [29, 30].

Viral reactivation may occur spontaneously but is most likely after stress, for example, moving a cat into a boarding cattery, to a cat show, or to stud [39]. Experimentally, the spontaneous viral shedding rate in clinically recovered carrier cats as assessed using virus isolation is about 1%; corticosteroid treatment may induce shedding in approximately 70% of cats, a change of housing in 18%, and lactation in 40% [23, 30, 34]. Episodes of detectable virus shedding do not immediately follow the stress. A lag phase of 4–11 days (mean 7.2 days) precedes the shedding of infectious virus, which ranges in duration from 1–13 days (mean 6.5 days) [29, 30]. In some cases, carriers show recrudescence of mild clinical signs while they are shedding, which can be a useful indicator that they are likely to be infectious [39].

In practical terms this means that if a cat experiences a stress, such as going into a boarding cattery, then it is likely to shed infectious virus in the 3-week period following this event. This tendency of the virus to reactivate when the cat moves into a different environment obviously confers a useful biological advantage in terms of transmission to new hosts. Similarly, shedding during lactation is an ideal mechanism for the virus to pass into the next generation of susceptible kittens. Whether the kittens develop disease depends on their levels of maternally derived antibody (MDA), but in some cases, kittens may be infected subclinically from their dam and become latent carriers under the protection of MDA [34].

The mechanism of stress-induced viral reactivation is not clear. Whatever the event or series of events that lead to the presence of detectable virus however, it seems probable that the immune response plays a role in determining the duration of the shedding episode. Interestingly, in studies of cats in which FeHV-1 reactivated after the natural stress of re-housing, it was found that cats that did shed virus (i) had experienced significantly more severe primary disease than those that did not; (ii) had a significantly greater 'stress' response (i.e. loss of appetite and nervous withdrawal) to re-housing than those that did not shed; and (iii) had a trend towards lower mean serum antibody levels (as assessed by antibody/complement lytic capacity) prior to re-housing compared to the non-shedder cats [36, 40]. There is also some evidence of a refractory period after an episode of viral reactivation when animals are less likely to shed [29, 30, 80].

It is probable that, as in other alphaherpesvirus infections, virtually all clinically recovered cats are carriers. However, less than half of these are likely to be of epidemiological importance, i.e. shed virus under natural conditions, and even then, transmission to susceptible animals is not necessarily easily achieved [30, 34]. More recent studies using PCR, including real-time PCR, have shown a higher sensitivity for detecting carriers, with a more prolonged presence of viral DNA in the secretions of infected cats [8, 45, 83, 111, 125, 131, 141, 146, 147]. Whilst such molecular techniques help identify carriers, the epidemiological significance of cats in which

viral genome can be detected by PCR, but from which infectious virus cannot be isolated is not clear, as transmission studies have not been performed. Although PCR is more sensitive than virus isolation, it has also been shown that the published techniques vary considerably in sensitivity [83]. Further, as FeHV-1 can be shed by clinically normal cats as well as diseased animals, a higher detection rate does not necessarily correlate with disease causation.

These experimental studies on the effects of stress associated with re-housing on inducing virus reactivation and shedding have also been translated to the field. In one study, 3 of 75 cats monitored over a one month period reactivated virus 9–12 days after entering a boarding cattery, and showed mild clinical signs [36]. In two more recent studies in shelter cats, FeHV-1 shedding rose markedly approximately one week after admission [1, 104], and although some of this may have been from cross-infection, it is likely that reactivating carriers were contributing significantly to these increased shedding rates. Several epidemiological studies have found a number of risk factors associated with FeHV-1 shedding, including contact with other cats, the presence of upper respiratory disease, younger cats, poor hygiene, and larger households; in contrast, vaccination is associated with a negative (i.e. protective) effect against viral shedding [3, 51, 132].

4. CLINICAL SIGNS

FeHV-1 infection generally causes severe upper respiratory disease in susceptible animals. The incubation period is usually 2 to 6 days but may be longer, and disease signs may be milder, with lower levels of challenge virus [33].

In both experimental and natural infections, early signs include depression, marked sneezing, inappetence, and pyrexia, followed rapidly by serous ocular and nasal discharges [15, 39, 56]. These initial clinical signs may be accompanied by excessive salivation with drooling. Conjunctivitis, sometimes with severe hyperemia and chemosis, typically develops, and there are copious oculonasal discharges. These gradually become mucopurulent, and crusting of the external nares and eyelids can occur. In severe cases dyspnoea and coughing may also develop. Oral ulceration can occur with FeHV-1 infection but is relatively uncommon compared to feline calicivirus (FCV) infection, the other main cause of viral respiratory disease in cats [39]. Occasionally, generalized infections and primary viral pneumonia may occur, particularly in young or debilitated animals [74, 119, 122, 139]. Neurological signs have been described, but appear to be a very rare sequel to infection [31].

Although abortion may be associated with other alphaherpesvirus infections, experimental studies have suggested that in cats infected with FeHV-1, abortion is most likely due to the severe systemic effects of the illness, rather than a direct effect of the virus itself [58]. Indeed, in an investigation of a natural outbreak of FeHV-1 infection in specific pathogen free cats, no cases of abortion were seen, even in severely affected pregnant queens [53].

Involvement of FeHV-1 in conjunctivitis and in some cases, ulcerative keratitis, has long been known [4], but improved viral detection using PCR has led to increased recognition of this role in the acute disease, and also in more chronic ocular lesions such as stromal keratitis [95,124,125, 128, 142]. The role of FeHV-1 in other ocular conditions such as corneal sequestrae, eosinophilic keratitis, uveitis and keratoconjuncitivitis sicca is however less clear and needs further evaluation [78, 97, 124, 128, 142].

Skin ulcers have been reported in the past with FeHV-1 in domestic cats and also in cheetahs [26,63,65]. More recently, an ulcerative facial and nasal dermatitis and stomatitis syndrome characterized by eosinophilic infiltration, which is occasionally persistent, has been described in a series of cats [49, 50], with a similar syndrome also being reported in cheetahs [91]. The role of FeHV-1 and the utility of PCR in the diagnosis of herpetic dermatitis has recently been shown by Holland et al. [55].

A possible role for FeHV-1 in chronic gingivostomatitis in cats has also recently been suggested, on the basis of a relatively high viral isolation rate from cases compared to controls [73]. However a similar number of cats were also shedding FCV, and previous studies have generally detected FCV rather than FeHV-1 from cats with this syndrome [66,110,133,136,145].

Because of the propensity of FeHV-1 to replicate in the turbinates during the acute phase of disease, and in the early stages of reactivation, a role for FeHV-1 in chronic rhinitis has also been considered. However a recent study has found no difference in detection rates between a small number of cases and controls [61] (see Section 2).

5. TREATMENT

Numerous nucleoside analogs have been developed with activity against human herpesviruses, mainly herpes simplex and varicella-zoster viruses. Several of these compounds have been also tested against FeHV-1, largely in vitro, though some limited clinical and experimental cat studies have been carried out. Acyclovir, which is widely used in human medicine, does not seem to have good activity in vitro against FeHV-1 [81,92,138,148,152] and both acyclovir and the acyclovir prodrug valacyclovir, are too toxic at therapeutic levels for oral administration to cats [96,102,126]. However, a number of other antiviral agents such as ganciclovir and cidofovir appear to have greater efficacy in vitro against FeHV-1, and may prove to be useful clinically [81,114,138].

The current treatment of FeHV-1 keratitis is therefore based on the topical use of nucleoside analogues. Trifluridine, idoxuridine, vidarabine, and to a lesser extent acyclovir have all been suggested as possible topical treatments for FeHV-1 ocular disease, though efficacy is difficult to assess in the absence of large-scale clinical trials [13,123,128]. Although acyclovir is less efficacious in vitro than vidarabine, idoxuridine, and trifluridine [92], in some countries it may be the most readily available, and may have some beneficial effect on FeHV-1-induced conjunctivitis and keratitis when applied frequently [152].

In vitro studies have shown that FeHV-1 is susceptible to feline interferon (IFN) or recombinant human IFN-alpha, and that the effect of acyclovir and recombinant human IFN-alpha is synergistic [27,115,148]. Although the authors are aware of no data from controlled clinical trials, it has been suggested that interferon may be useful for cats with either acute respiratory herpesvirus infection, or ocular disease [13, 128]. Feline omega interferon is now registered in Europe as an antiviral drug against feline leukemia and feline immunodeficiency viruses [19]. Some clinicians are starting to use this to treat FeHV-1 keratitis, but as yet no controlled trials have been undertaken.

The effect of L-lysine on FeHV-1 replication has recently been explored both in vitro and in experimental cat studies [79, 80, 127]. L-lysine is an antagonist of arginine, which has been shown to be essential for human herpes simplex virus and FeHV-1 replication [80]. Treatment with L-lysine therefore decreases viral proteosynthesis and has been shown to have some inhibitory effect against both human herpesvirus and FeHV-1 infection. Oral supplementation with L-lysine reduces the severity of experimentally-

induced FeHV-1 conjunctivitis when administered prior to primary infection [127] and the number of shedding episodes associated with reactivation of latent infection induced by re-housing [80]. It may therefore be of use early in acute disease or as a means of reducing the severity of disease and virus shed at times of stress: suggested dosage regimens are described elsewhere [82, 128]. There is evidence that dietary lysine supplementation is not effective in groups of cats and that maybe bolus administration is essential [84]. Bovine lactoferrin has shown some in vitro activity most likely by preventing attachment and penetration of FeHV-1 into susceptible cells [2], but in vivo efficacy has not yet been evaluated.

The use of broad-spectrum antibiotic therapy is advocated to help control secondary bacterial infection in cases of acute upper respiratory tract disease. Cats should be reexamined after 4 to 5 days and, if necessary, bacterial culture and susceptibility tests performed. Good nursing care is essential, and in milder cases is generally best given at home by the owner. Affected cats should be encouraged to eat by offering strongly flavored aromatic foods. If eating is painful, baby foods or specialized proprietary or blended food may be helpful. Severe cases may require hospitalization and fluid therapy, and when anorexia is prolonged a nasogastric or gastrotomy tube may be indicated. Nasal decongestants (e.g., phenylephrine) in the acute phase and mucolytic drugs (e.g., bromhexine hydrochloride) in the more chronic phase have been suggested to help clear airways, but conventional steam inhalation (e.g., placing the cat in steamy room) or nebulizing saline may also be useful.

6. DIAGNOSIS

Diagnosis may be based initially on clinical signs. FeHV-1 generally induces more severe upper respiratory tract and conjunctival signs than other feline respiratory pathogens, but where specific diagnosis is required, laboratory tests should be carried out for confirmation.

Although FeHV-1 is shed in oropharyngeal, conjunctival and nasal secretions, unless ocular disease is specifically being investigated, oropharyngeal swabs are generally used for diagnosis. Traditionally such swabs are placed in viral transport medium and inoculated into feline cell cultures where the presence of FeHV-1 can be identified by its characteristic cytopathic effect. Immunofluorescence, particularly of conjunctival smears, has also been used [9, 125].

In many laboratories PCR is now being used rather than culture. PCR, which targets specific regions of the genome, demonstrates that viral DNA is present in the swab, rather than the presence of infectious virus. PCR is generally more sensitive than virus isolation, detecting virus for longer in the acute stages of the disease, and in more chronic stages [124, 125, 131, 141, 146]. However, a comparison of the various PCR tests available does show considerable differences in sensitivity between the published tests [83].

Interpretation of the clinical relevance of detecting virus in a cat either by isolation or by PCR can be problematic [39,83]. If cats are showing characteristic clinical signs of acute FeHV-1 induced-disease, a positive sample can strongly support the diagnosis, particularly where cats are positive by virus isolation as well as by PCR. However, since virtually all clinically recovered cats become latent viral carriers which intermittently may shed virus, it is always possible that a positive result is an incidental finding unrelated to any presenting clinical signs, or is a result of the stress from another disease or other process. In an epidemiological context, however, any positive result indicates that the cat has been infected with FeHV-1, and as such is likely to be a carrier with the potential to

infect other animals. In countries where intranasal vaccines are available, a positive result, either by virus isolation or by PCR, may also be indicative of vaccine virus rather than wild-type virus: clearly the introduction of marker vaccines would help distinguish between these two possibilities.

7. IMMUNITY

Immunity to FeHV-1 has generally been measured by serum virus neutralizing (VN) antibody levels, although as for other alphaherpesviruses, cell-mediated immunity is likely to be a better reflection of immune status. Local immune responses are also likely to be important [11]. The ultimate test of immunity is, of course, response to challenge with infectious virus.

After primary FeHV-1 infection, cats are largely resistant to disease following further challenge but after six months or more, protection may only be partial [30, 143]. VN antibody titers are generally low and in some cases undetectable after primary infection, but after further exposure to virus, they tend to rise to more moderate levels and thereafter remain reasonably stable. Immunity following vaccination is considered below.

MDA to FeHV-1 is essentially colostral in kittens and generally persists for 2 to 10 weeks, with mean titres falling below detectable levels (< 1:2) by nine weeks of age [34]. However, there is considerable individual variation. In a more recent study, 25% of kittens had antibody titres of < 1 in 4 at six weeks of age, and such kittens may respond to early vaccination [18]. However, in some individuals, MDA may still be at interfering levels at 12–14 weeks of age [18, 72]. It should also be noted that low levels of MDA do not necessarily protect against subclinical infection and latency [34].

8. VACCINATION

Vaccination against FeHV-1 has been available for a number of years and has been relatively successful in controlling disease. However, disease can still be a problem, especially when cats are kept grouped together and when kittens lose their MDA before vaccination can take effect. Infection is widespread in the cat population and carriers are common, ensuring many opportunities for exposure particularly in situations that might precipitate shedding – e.g., change of housing or kittening and lactation. Prevention and control, therefore, often require a combined approach of vaccination and management.

Several types of FeHV-1 vaccines are commercially available and they are invariably given in association with FCV vaccines. Both modified live virus (MLV) vaccines and adjuvanted inactivated virus vaccines given parenterally are widely available; in some countries intranasal MLV vaccines are also marketed. All types of vaccine induce reasonable protection against disease in previously unexposed cats. However, none of the vaccines appears to protect against infection or the development of the carrier state, although both viral shedding and latency load of wild-type virus after viral challenge may be reduced in vaccinated cats compared to unvaccinated controls [28, 70, 99, 100, 130, 147]. Although intranasal vaccine virus can become latent [147], the situation with parenterally vaccinated cats is still unclear [130]. Whether vaccination helps control reactivation of already latent virus is not known, though parallels with other alphaherpesviruses suggest that this might be the case [7].

FeHV-1 vaccines are generally safe, and although occasional mild transient clinical signs can follow their use, in most instances it is not clear if this is due to the FeHV-1 or the FCV component [37, 38]. Mild transient signs have been reported

following experimental subcutaneous inoculation of an FeHV-1 vaccine strain [68], and most conventionally attenuated FeHV-1 vaccines do retain the capacity to induce disease if inadvertently administered via the oro-nasal route [68, 106, 107]. Thus care should be taken to ensure that the cat does not lick the injection site and that the veterinary surgeon does not make an aerosol of the vaccine with the syringe. For further investigation of such situations it would be helpful to have a reliable molecular typing system, or alternatively marker vaccines, to enable differentiation between vaccine and field viruses. However, such a system is not currently available.

Intranasal MLV vaccine induces better protection but often induces some mild side effects, such as transient sneezing and occasionally other clinical signs [70, 100]. Intranasal vaccines, however, are useful for rapid onset of protection, with partial protection seen after 2 days and significant protection after 4 and 6 days [10, 11, 70]. Intranasal vaccines used in conjunction with parenteral vaccine on entry into shelters have reduced the severity of upper respiratory disease in such establishments [21]. They have also been advocated for use in young kittens, to induce protection in the face of MDA, although there is evidence that some injectable vaccines may also be effective at an early age [18,36,64].

Inactivated adjuvanted vaccines can be reasonably effective, and modern adjuvants have led to improvements in immunogenicity. However, adjuvanted vaccines cause a significantly higher proportion of injection site reactions in comparison with MLV vaccines, although the actual reporting rate is still relatively low [37, 38]. Very rarely, sarcomas may develop at the site of injection, particularly following the use of aluminium-based adjuvants [37, 38, 75, 90]. Inactivated vaccines are helpful in virus-free colonies because there is no risk of spread or reversion to virulence. Some inactivated vaccines are licensed for use in pregnant queens, and vaccination during pregnancy can help protect kittens by prolonging MDA [60].

The issue of duration of immunity for FeHV-1 vaccines is of practical importance in that it determines appropriate vaccination intervals for cats. Traditionally, vaccination has taken place annually and in the EU, this is still the data sheet recommendations. However in the USA, vaccination guidelines are proposed by various scientific authorities, and largely because of concerns over adverse effects such as vaccine-associated sarcomas, triennial vaccination is now being recommended after the first annual booster [112, 113]: at the time of writing, a vaccine marketed in the USA now has this claim. Both in the USA and the EU it has also been proposed that an individual risk-benefit assessment should be carried out to determine the most appropriate vaccination strategy for a particular animal [37, 38, 112, 113] (EU guidance note EMEA/CVMP/205/03). Thus in cats with a previously low risk of exposure going into a high risk situation such as a boarding or rescue shelter for example, annual vaccination might still be considered appropriate.

Despite the trend towards increasing the vaccination interval, information on the duration of immunity following FeHV-1 vaccination is relatively limited. Although the majority of cats are protected against disease following the use of modified live or inactivated FeHV-1 vaccines, a proportion of cats will still show mild signs, even if challenge takes place within 3 months of the initial vaccination [6, 64, 99, 109, 116, 155]. However a significant reduction in overall clinical scores can generally be shown in vaccinates compared to controls, although the level of protection does decrease as the vaccination interval increases. Thus in studies with an inactivated vaccine, the relative efficacy was shown to decrease from 95% shortly after primary vaccination, to 52% after 7.5 years [109, 118].

The use of in vitro correlates of protection, such as virus neutralising antibody, to determine the level of protection would be useful, but as VN antibody titres are often low and sometimes undetectable, and because cell mediated immunity is also important, antibody tests do not necessarily accurately predict whether disease, or indeed what level of disease, will occur following FeHV-1 challenge. A recent study however showed a reasonable correlation in that most cats with detectable FeHV-1 antibodies (91% for VN antibodies; 90.5% for ELISA) had a greater than 50% reduction in clinical signs compared to controls. In contrast, two of three cats with no detectable VN antibody were reported to be susceptible to disease [69].

A number of attempts have been made to try to improve FeHV-1 vaccines, through genetic engineering. Thus recombinant poxviruses and baculoviruses have been constructed expressing the FeHV-1 glycoprotein D to characterize its properties and potential as an immunogen [77, 120]. A number of FeHV-1 deletion/insertional mutants have been developed including thymidine kinase deletion mutants, some of which have incorporated other genes including the FCV capsid gene [12, 88, 89, 144, 156–159]; gE-gI deletion mutants [68, 129, 130]; a gI insertional mutant (which also appeared to affect the transcription pattern and expression of the upstream gene gD) [150, 151]; and an insertional mutant of 'ORF2', downstream of glycoprotein C [149]. In general, these deletion/insertional mutants are less virulent for cats and offer some protection against disease, especially via the oro-nasal route. However, none has so far been marketed, probably because the protection offered is not superior to conventionally attenuated vaccines. In some cases – for example those containing deletions in non-essential genes such as the gE-gI deletion mutants – such vaccines do offer some utility as potential marker vaccines.

9. DISEASE CONTROL

Disease prevention and control should be approached through a combination of vaccination and management. Since FeHV-1 infection is highly prevalent, easily transmitted and disease can be relatively severe, vaccination of all animals is recommended. However the risk for each individual cat and situation should be assessed by the veterinary surgeon in consultation with the owner, so that an informed choice can be made about the frequency of vaccination [37, 38].

9.1. Household cats

Pets should be vaccinated regularly, but the re-vaccination intervals should be evaluated depending on the risk of exposure. If the cat goes into a boarding cattery or enters other high risk situations it should be vaccinated every year; otherwise after the first annual vaccine, triennial vaccination may be sufficient. To reduce exposure to such environments, ideally a friend or neighbour should feed the cat while the owner is on holiday. Individual cats should be protected from stress as much as possible to avoid exposure and reactivation from carriers.

9.2. Boarding catteries

All cats entering the cattery should have an up-to-date vaccination record. Since entering a boarding cattery is a high risk situation, annual vaccination is recommended. Where rapid protection is required (i.e. in the face of an outbreak of disease) intranasal vaccine may be given in countries where this is available; otherwise a MLV injectable vaccine is likely to induce a more rapid response than an inactivated one. Clients should be aware that intranasal vaccines themselves may induce mild clinical signs.

Cattery owners should not rely on vaccination alone for disease control, because pathogens will inevitably be present either from the occasional cat incubating disease or from reactivating carriers. Thus, measures should be taken to prevent spread of infection and reduce the concentration of infectious agents in the environment [39]. Such measures may appear complicated, but in practice they are not difficult to implement and, in our experience, can actually increase efficiency within a cattery.

9.3. Shelter facilities

In general, the same management measures apply as with boarding catteries. Since the immune status of the cats in a rescue shelter is often unknown, in-coming animals should be quarantined and isolated from others. Those with clinical signs should be kept apart from clinically normal animals. Unless animals can be isolated on arrival for 3 to 4 weeks, parenteral vaccines may not have time to become effective. In these circumstances, it may be advisable to use the intranasal vaccines if available; otherwise MLV injectable vaccines are advocated.

9.4. Breeding catteries

In disease-free colonies, cats should be vaccinated regularly if there is any contact, direct or indirect, with other cats. Inactivated vaccines are preferable. Care should be taken to avoid bringing virus into the colony; any cat with a history of, or contact with, oral or respiratory disease may be a carrier. Vaccinated cats can be carriers, and kittens can be infected subclinically under the protection of MDA. Thus, stud cats and new breeding stock should be from a respiratory disease-free colony. There is a possible risk of infection from cat shows, but the greatest risk of infection to disease-free households is from stud cats and new breeding stock when exposure is prolonged.

Cats entering a disease-free colony should be quarantined for three weeks to identify animals incubating the disease. Swabs should be collected from each cat at least twice a week during this time, and evaluated for the presence of FeHV-1. If possible, PCR should be used rather than virus isolation, because of the former's greater sensitivity. However, even with negative results, there is still the risk of importing a latent FeHV-1 carrier that may subsequently be a source of infection.

In breeding colonies where the disease is endemic, it is difficult to achieve or maintain virus free status. For most situations, the only reasonable course is to attempt disease control, largely by ensuring queens are regularly vaccinated, reducing stress, isolating queens and their kittens, and considering early weaning kittens into isolation or initiating kitten vaccination at an earlier age [18, 39]. In some cases, it may be necessary to reduce the number of cats in the colony.

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